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ORAL AND HEAD AND NECK CANCER

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This **SPECIAL LISTING** of Current Cancer Research Projects is a publication of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) Program of the National Cancer Institute. Each **LISTING** contains descriptions of ongoing projects in one selected cancer research area. Approximately 55 areas are covered in separate **SPECIAL LISTINGS.** Each title of these **SPECIAL LISTINGS** is published annually.

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CURRENT CANCER RESEARCH

I. HUMAN CANCER ETIOLOGY AND EPIDEMIOLOGY

A. ROLE OF VIRUSES

1. SEROEPIDEMIOLOGICAL STUDIES ON NASOPHARYNGEAL CARCINOMA AND BURKITT'S LYMPHOMA

Linsell, C. A., Centre International de Recherche sur le Cancer, *150 Cours Albert Thomas, 69372 Lyon Cedex 2, France*

SCOPE: Research activities aimed at studying the association between EBV, Burkitt's lymphoma and NPC.

Results will be helpful in defining the viral etiology of various types of human cancer and in defining approaches for this control.

The studies under this contract are being developed as three projects: 1. The prospective study in Africa (Uganda) to determine the serological status of African children in relation to EBV. 2. The epidemiology of EBV in different population groups. 3. Studies on the etiology of nasopharyngeal carcinoma.

2. THE SEROEPIDEMIOLOGY OF THE EPSTEIN-BARR VIRUS (EBV)

Henle, W., Klein, G., Olweny, C. L., Nkrumah, F. K., Ziegler, J. L., De The, G., Lanier, A. K., Ho, C. H., Children's Hospital of Philadelphia, Division of Virology, *3400 Civic Ctr. Blvd., Philadelphia, Pennsylvania*, 19104, United States of America

The aims of this study are (1) to provide further evidence for an etiological role of EBV in Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC), (2) to relate the spectra and titres of antibodies to EBV-determined antigens with the clinical status, the prognosis and the effectiveness of therapy of these two malignancies, (3) to ascertain the antibody status prior to the development of BL in a prospective study of BL in the West Nile district of Uganda, (4) to determine the effects of immunosuppressive diseases, such as Hodgkin's disease, or of immunosuppressive therapy, as used in case of organ transplant patients, on latent, persistent EBV infections and the EBV-related antibody patterns, (5) to evaluate the demonstration of EBV-associated nuclear antigen in the carcinoma cells of NPC biopsies as an aid in the diagnosis of this malignancy.

3. VIRUS ETIOLOGY OF HUMAN MALIGNANT DISEASE - LYMPHOMA/NASOPHARYNGEAL CARCINOMA

Epstein, M. A., Rickinson, A. B., Wallace, L. E., University of Bristol, School of Medicine, Dept. of Pathology, *University Walk, Bristol BS8 1TD, England, United Kingdom*

OBJECTIVE: To investigate the relationship of Epstein-Barr virus to the two human tumors with which it is associated, endemic Burkitt's lymphoma and undifferentiated nasopharyngeal carcinoma, and to compare this relationship with that of the virus to cells of the huge number of normal individuals who carry the virus for life without clinical consequences.

APPROACH: Cell-virus interactions are under study comparing the relationships in the malignant cells of Burkitt's lymphoma and the malignant cells of nasopharyngeal carcinoma; attempts are being made both to infect normal nasopharyngeal epithelium and to establish continuous cell lines of malignant nasopharyngeal carcinoma.

In addition, the cellular immunological controls operating in normal individuals infected by Epstein-Barr virus are being investigated and the role of specific memory T cells has been established. Specific T cell function is being studied in patients with Burkitt's lymphoma both to determine whether this function is impaired in such cancer patients and to establish whether the tumor cells are able to escape in some way from the T cell-mediated cytotoxicity. Similar studies will be extended to nasopharyngeal carcinoma.

4. EBV VIRUS POPULATIONS AND THEIR ASSOCIATION WITH INFECTIOUS MONONUCLEOSIS, BURKITT'S LYMPHOMA AND NASOPHARYNGEAL CARCINOMA

Mitrani Rosenbaum, S., Ben Bassat, H., Goldblum, N., Klein, G., Hebrew University of Jerusalem, Hadassah Medical School, Chanock Centre for Virology, *P.O. Box 1172, Jerusalem 91000, Israel*

Cases of infectious mononucleosis (IM) and biopsy material from Burkitt's lymphoma (BC) and nasopharyngeal carcinoma (NPC) are being collected from various parts of the world (Israel, Europe and Africa). The isolated populations are being characterized according to a number of biological properties, such as in vitro infectivity, transformation of lymphocytes into permanent lymphoblastoid lines, conversions of EBV-negative lines into EBV-genome carrying, suspectible lymphocytes, etc. The purpose of this study is to examine whether EBV isolates from cancerous and non-cancerous sources differ in their biological properties and, if so, whether the specific activities are associated with distinct strains of the virus or are related to target cell. Preliminary results indicate that EBV isolates from IM patients are very efficient in transformation of lymphocytes into lymphoid lines but very weak in conversion of EBV negative Burkitt cell lines into EBV-carrying cells. EBV isolates from lymphoblastoid lines established from NPC patients were less efficient than IM-EBV in transforming lymphocytes but more so than EBV isolates obtained from Burkitt's lymphoma lines. These results indicate differences between EBV strains from various sources. The transformation and conversion experiments indicate that the differences observed may be related to both the EBV-isolates and to target-cell relationship.

5. EPSTEIN-BARR VIRUS DNA IN NASOPHARYNGEAL CARCINOMAS OF NORTH AMERICAN ORIGIN

Pagano, J. S., Traub, N. R., University of North Carolina, Chapel Hill Campus, School of Medicine, Dept. of Bacteriology & Immunology, *Manning Dr., Chapel Hill, North Carolina*, 27514, United States of America

We wish to determine the complexity of Epstein-Barr virus homologous DNA in nasopharyngeal carcinoma biopsies and to identify those restriction enzyme fragments of laboratory viral strains that are homologous to it. Epstein-Barr virus (EBV) is linked to three human diseases: infectious mononucleosis, Burkitt's lymphoma, and nasopharyngeal carcinoma. Each disease is predominant in a different geographic location. Therefore a central question in EBV research is whether the strains of virus isolated from the different niches differ from one another.

Previous work has shown that one strain of virus, an infectious mononucleosis isolate, has a deletion of sequences that are present in three Burkitt lymphoma viral strains. The deletion has been mapped to specific restriction enzyme fragments. These deleted sequences are transcribed in primary Burkitt tumors. The presence of these sequences and the extent of transcription in nasopharyngeal carcinoma tissue have yet to be determined. Our approach to test for the presence of EBV homologous sequences and to estimate their sequence complexity will be to analyze the kinetics of hybridization of 32P labeled EBV DNA and nasopharyngeal carcinoma DNA. To obtain a more accurate estimation of complexity and to map which specific sequences are present, we will separate viral from cellular sequences by several cycles of isopycnic buoyant density gradient centrifugation. These sequences will then be labeled in vitro by nicked translation with E. coli polymerase I and hybridized to Southern blots of known viral laboratory strains. RNA will be isolated as described, and hybridized to 32P labeled viral probe. DNA:RNA hybrids will be extensively digested with S1 nuclease to digest unhybridized DNA, purified on cesium sulfate gradients, and hybridized to Southern blots of viral DNA. This will identify those DNA fragments which are homologous to the sequences that are transcribed in nasopharyngeal carcinomas.

6. ASSOCIATION OF EPSTEIN-BARR VIRUS WITH NASOPHARYNGEAL CARCINOMA IN AMERICAN CHILDREN

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Following the demonstration of an association of Epstein-Barr virus (EBV) with nasopharyngeal carcinoma (NPC), the proposed investigation aims: (1) To determine whether there exists any serological association of EBV with NPC in American children. Since carcinoma is rare in childhood, an association with EBV may be of etiological significance. (2) To determine the relationship of EBV-related antibody spectra and titres to the stage of the disease. (3) To demonstrate the presence of EBNA or EB viral DNA in carcinoma cells from fresh NPC biopsies. Since 1962, 18 children with NPC have been admitted to St. Jude Children's Research Hospital; 11 diagnosed from 1 to 12 years ago are still surviving. This present patient population will serve as the base for the proposed study. The antibody status to EBV-determined antigens will be determined on serial serum samples and in conjunction with the demonstration of EBV genome in carcinoma cells should provide information concerning the association of EBV with this rare non-endemic pediatric carcinoma.

7. IMMUNOLOGICAL AND MOLECULAR HYBRIDIZATION STUDIES OF NASOPHARYNGEAL CARCINOMA

Ablashi, D. V., Aaronson, S., O'Conor, G., Levine, P., Prasad, U., Bengali, Z., Armstrong, G., Allouache, A., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Laboratory of Cellular & Molecular Biology, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

Epstein-Barr virus (EBV) is considered a major factor in nasopharyngeal carcinoma (NPC). The study aims to further assess the role of EBV in terms of etiology, diagnosis/prognosis and other environmental and genetic factors essential in defining the populations and individuals at risk. Studies include EBV-serology (humoral and cell-mediated), virology (attempts to isolate EBV and to compare it with known EBV isolates) and attempts to propagate epithelial cells from biopsies, examination of the HLA profile of cases, detection and examination of EBV genome expression in biopsy material by nucleic acid hybridization, review of the histopathology of all such cases and an attempt to prepare somatic cell hybrids to detect EBV receptors. Malaysia has a high incidence of NPC and has subpopulations consisting of Malayans, Indians and Chinese, whereas West Germany and the USA are low NPC incidence areas. However, in the USA, NPC cases include Chinese, white and black populations and Alaskan Eskimos. In Algeria NPC ranks as the number four cancer in males. There are also two age peaks in this population. Since NPC occurring at a young age has been observed in the black population in some southern states of the USA, Algerian NPC would provide an excellent comparison. Histopathological slides from West German and American NPC cases have been circulated for review to resolve differences in interpretation. Examination of approximately 14 cases of German NPC and more than 30 cases from Algeria suggests that antibodies to EBV antigens are much higher in Algerian cases. Data also show that antibodies to EBV are higher in American than in West German NPC. Attempts to propagate epithelial cells from NPC biopsies in vitro were unsuccessful.

8. IMMUNOGENETIC AND IMMUNOLOGICAL ASPECTS OF NASOPHARYNGEAL CARCINOMA (NPC)

Chan, S. H., Levine, P. H., Shanmugaratnam, K., Day, N. E., University of Singapore, School of Medicine, Dept. of Microbiology, *Sepoy Lines, Singapore 3, Singapore*

HL-A profiles associated with risk of development of NPC and with prognosis have now been established. The haplotype A2 BW46 (Sin 2) is associated with a relative risk (RR) of 1.97 and 2.29 in two studies of newly diagnosed NPC patients. Another haplotype, AW19 B17, is associated with a RR of 2.80 and 2.60 in the two studies. AW19 B17 and, to a lesser extent, A2 BW46 have been found to be associated with poor survival in a restrospective study. HL-A - DR locus antigen typing in NPC patients has begun. NPC patients showed a higher frequency of DR locus blank antigen than controls. A local DR antisera, AH21, showed higher reactivity among the patients than controls (RR equals 8.0). A prospective study of HL-A profiles and prognosis in NPC is in progress. A prospective study of HL-A, Epstein-Barr virus serology and development of NPC in a normal population has also been started.

9. EPSTEIN-BARR VIRUS AND NASOPHARYNGEAL CARCINOMA

Glaser, R., Ohio State University, Columbus Campus, School of Medicine, Dept. of Medical Microbiology, *370 W. 9th Ave., Columbus, Ohio,* 43212, United States of America

OBJECTIVES: Studies on the infection by Epstein-Barr virus (EBV) of normal human epithelial cells, particularly nasopharyngeal cells; cellular hybridization studies with an HR-1 cell line containing one EBV genome per cell; studies on the transformation of normal human primary epithelial cells with EBV by a nuclear exchange procedure; studies on in vivo cell fusion of EBV genome positive lymphoid cells and nasopharyngeal cells.

10. THE RESCUE OF EB VIRUS FROM PRIMARY CULTURED CELLS OF NASOPHARYNGEAL CARCINOMA

Kawamura, A., Takada, M., Takei, M., Murata, M., Okumura, H., University of Tokyo, Inst. of Medical Science, Dept. of Immunology, *P.O. Takanawa, Tokyo, Japan*

Biopsied cells from a nasopharyngeal carcinoma (NPC) patient have been cocultivated with human cord lymphocytes of opposite sex.

As a result, transformation of lymphocytes is observed and these transformed lymphocytes are EBNA positive cells.

These facts confirm existence of EBV and EB genome in NPC cells and suggest an explanation for oncogenicity of EBV in the nasopharynx.

11. EPSTEIN-BARR VIRAL DNA CONTENT OF NASOPHARYNGEAL CARCINOMA (HUMAN)

Pagano, J. S., University of North Carolina, Chapel Hill Campus, School of Medicine, Dept. of Medicine, *Manning Dr., Chapel Hill, North Carolina,* 27514, United States of America

This is part of a broader project. A summary of this subproject is not available.

12. MONITORING OF HERPES SIMPLEX VIRUS TUMOR-ASSOCIATED ANTIGENS IN HUMAN MALIGANT NEOPLASIAS

Tarro, G., DiGioia, M., Battista, A., Smeraglia, R., Cocchiara, R., Flaminio, G., Papa, C., Universita degli Studi di Napoli, Cotugno Hospital, Dept. of Virology, *Quagliariello, Naples, Italy*

The detection of HSV nonvirion antigens in selected tumors as expression of a repressed viral genome proves a continuing release of virus specific messages and supports an important role of the virus in the development of the tumor.

The purification of nonvirion antigen induced by HSV facilitates the detection of antibody for HSV nonvirion antigens in patients with certain cancers without absorption of their sera with HSV virion antigens. Furthermore, the preparation of specific antibody for these special antigens (nonvirion) is now relatively at hand in many laboratories for the investigation of the immune response of cancer and control populations.

PURPOSES AND AIMS: 1. To obtain purified preparations of HSV tumor-associated ('nonvirion') antigens (TAA) for use in radioimmunoassay and ELISA with cancer and control sera. 2. To monitor the presence of specific TAA antibodies in patients with different tumors of the oral and urogenital tract. 3. To correlate the clinical stage of the neoplastic disease with the presence of antibody to HSV-TAA. 4. To determine the difference in the amounts of HSV-TAA antibody between pre-operative patients and those clinically cured.

13. RELATIONSHIP BETWEEN HERPES VIRUSES AND CERTAIN HUMAN MALIGNANCIES

Giraldo, G., Beth, E., Levine, D., Mike, V., Geser, A., Chernesky, M. A., Huraux, J. M., Claudio, F., Giordano, G., Ngu, V., Kyalwazi, S. K., Gharbi, R. M., Memorial Sloan Kettering Cancer Center, Immuno-Virology Section, *1275 York Ave., New York, New York*, 10021, United States of America

There is increasing evidence that herpes viruses play a role in the induction of some human cancers (e.g., EBV and Burkitt's lymphoma; nasopharyngeal carcinoma; HSV-2 and cervical cancer; CMV and Kaposi's sarcoma). The main objectives of the project are: (1) To establish an association between the above-mentioned viruses and malignancies by seroepidemiological studies in high and low risk populations; (2) to analyze whether susceptibility to skin cancer can be shown by immunogenetic studies (HLA and MLC) in a high risk population, Tunisian xeroderma pigmentosum patients; (3) field studies in high incidence areas of Kaposi's sarcoma to detect time-space clusters; (4) retrospective analyses of Kaposi's sarcoma patients to determine if Kaposi's sarcoma is more often associated with a second primary cancer than other cancers. Seroepidemiological studies establish the antibody profile against early and late antigens for herpes viruses in cancer patients and controls. Kaposi's sarcoma cases derive from Uganda, Cameroon, Tunisia, France, USA and Italy; skin cancer from xeroderma pigmentosum patients in Tunisia; penile carcinoma from Uganda. Two sex-matched and age-matched (plus or minus 2-5 years) healthy subjects, living in the same areas and in similar socioeconomic conditions, will be used as controls. A second control group will consist of serum samples from age- and sex-matched patients with a cancer of different origin and location but similar therapy.

14. CELLULAR TRANSFORMATION BY DNA OF HUMAN HERPESVIRUSES

Hayward, G. S., Hayward, S. D., Reyes, G. R., LaFemina, R. L., Johns Hopkins University, School of Medicine, Dept. of Pharmacology & Experimental Therapeutics, *725 N. Wolfe St., Baltimore, Maryland*, 21205, United States of America

The herpesviruses are the largest and most complex of the known oncogenic DNA viruses. Three human herpesviruses have been implicated as possible contributing factors in certain human tumors: Epstein-Barr virus in Burkitt's lymphoma and nasopharyngeal carcinoma, herpes simplex virus type 2 in cervical carcinoma and cytomegalovirus in Kaposi's sarcoma. The evidence for this rests primarily on epidemiological and serological associations: the long-term persistence of the viruses in a latent reactivable state in neurons and lymphocytes of most individuals and the ability of the viruses to transform normal primary cells into permanently growing or malignant cells in culture.

We have been mapping and studying the structure of the large DNA molecules from these viruses with the long-term goal of defining the detailed molecular mechanisms of morphological transformation by human herpesviruses. Specific isolated DNA fragments representing 5%-10% of the HSV-1 and HSV-2 genomes have already been shown to consistently initiate focus formation in monolayers of contact-inhibited cells. In some cases cell lines derived from these foci contain stably integrated fragments of viral genetic information. Under funding of this project we plan to (1) more precisely define the herpes simplex virus genes responsible for initiating focus-formation; (2) detect their RNA and protein products in the transformed cells and examine the novel linkage between viral and cellular DNA sequences; (3) identify a similar small 'transforming fragment' from cytomegalovirus DNA on which to concentrate our mapping studies; and (4) identify the fragment from Epstein-Barr virus DNA that codes for the EBNA antigen, a consistent viral marker expressed in Burkitt's lymphoma cells.

15. CYTOMEGALOVIRUSES AND HUMAN MALIGNANCY

Haung, E., Boldogh, I., University of North Carolina, Chapel Hill Campus, School of Medicine, Dept. of Medicine, *Manning Dr., Chapel Hill, North Carolina*, 27514, United States of America

The overall objective of this project is to investigate the causal association between human cytomegalovirus (human CMV) and various human malignancies, especially the virus and cell interactions that might bear upon the mechanism of herpesvirus oncogenesis. The long-term objectives are directed by the following approaches: a) Detection of the existence of human CMV genome in various cancer tissues by nucleic acid hybridization techniques. b) Observation of virus and cell interaction by transforming various mammalian cells with viruses isolated from various tumor tissues and detection of virus genome and virus message in transformed cells. c) Genetic analysis of human CMV strains isolated from various clinical manifestations. d) Designation of the viral DNA restriction fragment which is responsible for the virus oncogenesis.

16. ULCERATIVE LESIONS AND TUMORS - PAPILLOMAS OF ORAL CAVITY

Jenson, A. B., Notkins, A. L., Olson, C., Lancaster, W., Shah, K., Hawley, P., Pass, F., Wise, T., Shaffer, E., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Inst. of Dental Research, Laboratory of Oral Medicine, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

Papillomavirus antigens were detected in verruca, multiple papillomas, condylomata and laryngeal papillomas of the oral cavity by the peroxidase-antiperoxidase technique.

BIBLIOGRAPHIC REFERENCES: Jenson, A.B., Rosenthal, J.R., Olson, C., Pass, F., Lancaster, W.D., and Shah, K.: Immunologic relatedness of papillomaviruses from different species. JNCI 64(3): 495-498, 1980.

B. ROLE OF RADIATION

17. IRRADIATION-INDUCED HEAD AND NECK TUMORS

van Daal, W. A., Hermans, J., Goslings, B. M., van Vloten, W. A., Sepmeijer, C. F., Vink, M., Ruiter, D., Pauwels, E. K., Academisch Ziekenhuis Leyden, Dept. of Radiotherapy, *Rijnsburgerweg 10, 2333 AA Leyden, Netherlands*

OBJECTIVES: 1. Tracing and treatment of patients at risk for malignant tumors as a late effect of irradiation for benign diseases. 2. Calculation of dose-effect relationship for radiation-induced thyroid nodules. 3. Comparison of findings of palpation, scintigraphy and histologic examination for the resected thyroid glands. 4. Collection of data on the incidence of radiation-induced tumors of the skin, mouth, nasopharynx, salivary glands, parathyroids and other organs in the head and neck region.

APPROACH: The addresses and/or information on causes of death of 2480 patients, irradiated after 1932 for tuberculous lymph adenitis, hyperthyroidism, papillomas of the larynx, etc., are obtained from the population register offices. The technique of irradiation, dose and number of fractions received by all these patients are known from the original radiation records. Patients are requested to appear for examination of the head and neck organs. The thyroid is examined by palpation and technetium scintigraphy. If abnormalities are detected, further examination and treatment are advised.

PROGRESS: As of December, 1980, 25 percent of the cohort (605 patients) has been examined. These patients are divided in four categories: 1) 257 patients who showed up for clinical examination. 2) 179 patients who are deceased, with 85 percent known causes of death. 3) 87 patients who refused clinical examination. 84 percent of them supplied us with useful information concerning induced diseases. 4) 82 patients who could not be traced.

Every third clinically examined patient showed nodular thyroid disease. However, the number of thyroid carcinomas seems to be far less than expected.

18. IRRADIATION OF THE HEAD AND NECK

Cabrini, R. L., Carraro, J., Itoiz, M. E., Ubios, A., Lanfranchi, H. E., Dominguez, F. V., Universidad de Buenos Aires, Facultad de Odontologia, Catedra de Anatomia Patologica, *M.T. de Alvear 2142, 1122 Buenos Aires, Argentina*

OBJECTIVE: Various forms of radiotherapy are currently used for the control of the majority of malignant tumors. Recently, new methods of irradiation have been developed that involve the use of high-energy X-ray equipment and particulate irradiation combined with administration of chemotherapeutic agents. This has created some practical problems such as the many lesions which occur in the head and neck area after irradiation of tumors.

APPROACH: Using extensive experience in the basic mechanism of skin, mucosal and bone lesions caused by irradiation, basic and applied research is planned to determine the noxious effects of therapeutic irradiation and to attempt to control them in the future.

PROGRESS: The applied research will consist of study and follow-up of the oral clinical status of patients undergoing therapeutic irradiation, with special attention being given to periodontal damage. (Translated)

19. DOSE-EFFECT RELATIONSHIP OF LOW DOSAGE X-RAY THERAPY TO THE HEAD AND NECK AREA

Dean, G., Adelstein, A. M., Medico-Social Research Board, *73 Lower Baggot St., Dublin 2, Ireland*

Modan et al. showed that there was an increased mortality from certain cancers among those who had been treated as children with x-ray therapy for ringworm of the scalp (Lancet, I, 277-279, 1974). It is proposed to ascertain the mortality of those who were given superficial x-ray therapy to the head and neck area between 1928 and 1960 for acne and related conditions. Hospitals at Liverpool, Glasgow, Birmingham, Manchester, Leeds and London are collaborating in the study. The main conditions treated were acne, sycosis barbae, other skin conditions and eye conditions. It is expected that information will be obtained for about 10,000 patients treated. Follow-up will be achieved using the National Health Service Register in Southport to find deaths since the start of the National Health Service in 1948 and through the Area Health Authorities and the family doctors, to find those who are still alive in case further study is required at a later date. Both the National Cancer Register and regional cancer registers will also be checked. The study program will be completed in 1981/82.

20. PARATHYROID DISEASES ASSOCIATED WITH IRRADIATION

Tamura, K., Shimaoka, K., Spaulding, S., Shedd, D., Roswell Park Memorial Inst., Dept. of Medical Oncology, *666 Elm St., Buffalo, New York*, 14263, United States of America

There have been scattered reports showing that parathyroid adenoma and hyperplasia with hyperparathyroidism were associated with irradiation to the head and neck areas for benign diseases in childhood. To delineate this relation 50 documented cases with parathyroid adenoma or hyperplasia are being surveyed by mail questionnaire. The prevalence of hypercalcemia and hyperparathyroidism in more than 1,000 cases from the thyroid screening program where all that patients had radiation therapy for benign diseases in childhood or young adulthood, and in 300 patients with malignant lymphoma who have been treated with radiation therapy to the neck area, is also being examined.

21. RADIATION-INDUCED THYROID CANCER

Schneider, A. B., Frohman, L., Pinsky, S., University of Chicago, Michael Reese Hospital & Medical Center, Dept. of Medicine, *2929 S. Ellis Ave., Chicago, Illinois*, 60616, United States of America

The major objective of this research proposal is to study radiation-induced thyroid cancer by a coordinated program of clinical and basic endocrinological investigations. The clinical studies are designed to determine the current risk and continuing incidence of radiation-induced thyroid cancer and to evaluate methods of diagnosis and medical and surgical approaches to treatment. This will be accomplished by a longitudinal study of patients who have been evaluated at Michael Reese Hospital because of a history of childhood head and neck irradiation. Of 5,200 patients who were so treated, 1,700 have been examined and another 1,400 have been contacted. In this population there is a 32 percent prevalence of nodules and among those who have had surgery 36 percent have had thyroid cancer. Follow-up examination of patients who were initially normal will provide an estimate of the continuing incidence of radiation-induced thyroid cancer. Follow-up examination of patients who were initially abnormal will provide an evaluation of the various methods of treatment which have been used. Together these will provide the information necessary to develop clinical guidelines for the care of persons with a history of head or neck irradiation.

Laboratory studies will focus on the role of serum thyroglobulin in the diagnosis of thyroid tumors. Plasma thyroglobulin is elevated in a majority of patients with thyroid nodules and in 12 percent of patients who have a history of irradiation but who otherwise appear completely normal. This project will determine whether an elevated thyroglobulin level indicates an especially high risk for the formation of thyroid nodules and study the role of serum thyroglobulin measurements in managing patients with thyroid cancer.

Detailed studies of the molecular properties of serum thyroglobulin using physical-chemical methods will continue in order to improve its diagnostic usefulness and to understand how it enters the circulation. The mechanisms controlling thyroglobulin synthesis and secretion will be studied by perfusion of isolated thyroid cells and follicles. The Wollman transplantable thyroid tumor line 1-1C2 will be used as a model system to study plasma thyroglobulin and thyroid cancer.

BIBLIOGRAPHIC REFERENCES: Ikekubo, K., Pervos, R. and Schneider, A.B.: Clearance of Normal and Tumor Thyroglobulin from the Circulation of Rats: Role of the Terminal Sialic Acid Residues. Metabolism 29:673-681, 1980. Ikekubo, K., Jutton, J. and Schneider, A.B.: Radioimmunoassay of Human Thyroglobulin with Use of Thyroglobulin-free Plasma Prepared by Ultracentrifugation as Diluent. Clin. Chem. 26:1566-1568, 1980.

22. HUMAN RADIATION CARCINOGENESIS STUDY

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This application proposes continuation of long-term prospective studies of three well-defined populations irradiated for benign conditions: (1) persons whose thymus glands were irradiated in infancy; (2) persons given x-ray and/or radium treatments for hypertrophy of adenoidal tissue during childhood; and (3) women whose breasts were treated with x-rays for acute post-partum mastitis. The objective of the program is to determine the risk of radiation-induced disease (neoplasia, autoimmune and psychiatric illness) with particular attention to the dose-response relationship for neoplastic disease. A second objective is to detect (by periodic mammographic-thermographic screening) and treat early cases of breast cancer in a high-risk population (mastitis-irradiated series). Additionally, findings in the screening program will be evaluated for predictive significance.

The health of the irradiated subjects and their non-irradiated sibling controls is followed by mailed health questionnaire. Significant illnesses and operations are verified with the attending physician and/or hospital. Sections of neoplasms of selected sites (breast, thyroid, and salivary glands) are requested for review. The breast-irradiated women and eligible controls (NCI guidelines) will be offered annual mammographic-thermographic screening. Laboratory studies of B and T lymphocytes will be conducted on selected individuals in the thymus series. Additional dosimetry calculations will be performed for selected tissue sites in the head-irradiated series (thyroid, pituitary, and salivary glands) and thymus-irradiated series (breast tissue).

23. MANAGEMENT OF PATIENTS WITH A HISTORY OF IRRADIATION TO THE THYROID GLAND

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This series began in 1965 according to a protocol designed to determine the incidence of occult malignancies, bilaterality of cancers, and the potential long term, beneficial effects of otal thyroidectomy (in spite of added risks of permanent hypoparathyroidism and recurrent nerve palsy) in patients with thyroid nodules and a history of exposure to head and neck irradiation for benign diseases.

During the past year, 22 patients were added to this series, which now numbers 167. The incidence of carcinoma is approximately 43%, the incidence of multicentricity 40%, figures which are similar to our previous reports. A significant malignancy would have been overlooked in 6 patients, if total thyroidectomy had not been done. The incidence of permanent hypoparathyroidism and recurrent nerve palsy still stands at approximately 1%.

BIBLIOGRAPHIC REFERENCES: Paloyan, E. and Lawrence, A.M.: Thyroid neoplasms after radiation therapy for adolescent acne vulgaris. Arch. Dermatol. 114: 53-55, Jan. 1978. Paloyan, E., Prinz, Richard A., and Lawrence, Ann M.: Current Trends in Endocrine Surgery. Surgery Annual 12:205-222, 1980.

24. LONG-TERM FOLLOW-UP OF PERSONS EXPOSED TO SCALP IRRADIATION IN CHILDHOOD

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Approximately 11,000 individuals irradiated between 1948 and 1960, for control of tinea capitis, and two matched control groups (almost 16,000 people) are being retrospectively followed through national registries and medical records. The irradiated group has been found to have a significant excess of malignant and benign head and neck tumors, especially of the brain, parotid gland and the thyroid.

25. FOLLOW-UP STUDY OF PATIENTS TREATED BY X-RAY EPILATION FOR TINEA CAPITIS

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Children treated for tinea capitis between 1940 and 1959 at a major New York City dermatology clinic have been followed to examine the tumourigenic effects of X-radiation to the head (300 - 400 R). Some 2,215 irradiated patients and 1,395 patients given medications for tinea capitis have been traced. The groups are very well matched on sex, race, age and socioeconomic status. A third survey of these groups (average interval since tinea treatment - 20 years) is in progress and is showing a continued excess of basal cell carcinomas, and brain, thyroid and parotid tumors in the irradiated group.

26. EPIDEMIOLOGY OF TUMORS OF THE PAROTID GLAND

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We propose a case-control study to test the hypothesis that previous exposure to diagnostic dental X-rays and to other forms of radiation are causally related to tumors of the parotid gland. We will also evaluate the importance of other potential risk factors for this disease.

Cases include all types of parotid neoplasms (both benign and malignant) identified by the LAC/USC Cancer Surveillance Program over a five year period. A neighbor control of like sex, race and age (birth year within five years) will be selected for each case. Information on dental and medical X-rays, job exposures, family cancers and tobacco and alcohol use will be obtained through telephone interviews using a standard questionnaire. Interview information on dental X-rays will be validated for a subset of cases and controls by a review of dental record.

The relative importance of various exposures at different ages will be evaluated. Associations of tumor occurrence with radiation exposure and with smoking history will be analyzed separately for tumors of different histologic types.

27. PRIMARY SALIVARY GLAND NEOPLASMS IN ROCHESTER, MINNESOTA

Bouquot, J. E., Lovested, S. A., Weiland, L. H., Elveback, L. R., Kurland, L. T., West Virginia University, School of Medicine, Dept. of Oral Pathology, *Medical Ctr. Dr., Morgantown, West Virginia*, 26506, United States of America

An association between irradiation of the head and neck and subsequent development of benign and malignant salivery gland neoplasms has been noted in the literature. Most of these neoplasms have been benign. This study will provide such data for the Rochester population as well as detailed clinical information on the few neoplasms that are malignant.

28. A SURVEY OF LIP CANCER AND SOLAR CHEILOSIS IN THE STATE OF OKLAHOMA

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OBJECTIVES: The purpose of this study is to study the relationship of sun exposure and solar cheilosis with the carcinogenesis of lip cancer in the state of Oklahoma.

RESEARCH PLAN: The VA Medical Center, Oklahoma Memorial and Presbyterian Hospitals will provide the sample population for this study. The study will be a retrospective study utilizing selected patient information obtained from the Tumor Registry, University of Oklahoma Health Sciences Center.

METHODOLOGY: Information needed will be obtained by review of patient charts and by telephone interview. Also involved will be a review of pathological biopsy slides for determination of changes indicated by solar radiation.

SIGNIFICANCE: What the investigators hope to discover is a correlation between the neoplasia experience and occupational information provided by the patient.

C. ROLE OF ALCOHOL AND SMOKING

29. ROLE OF ALCOHOL AS PRIMARY RISK FACTOR IN ORAL CANCER

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The objective of this case-control study is to determine the significance of alcohol in the development of oral and pharyngeal squamous carcinoma and its relative risk compared to that of cigarettes. Our preliminary studies appear to indicate that alcohol may be a greater risk factor than tobacco and that beer and wine in particular appear to be significantly greater risk factors than whiskey. Patients admitted or identified as having squamous carcimoma of the oral cavity or pharynx will be entered into the study as cases. A history of alcohol comsumption, smoking habits, other upper aerodigestive tract cancers and other epidemiologic data shall be gathered for these patients via interview at the time of diagnosis. A control population without history or evidence or oral, pharyngeal or upper aerodigestive tract cancer (lung, larynx, esophagus) will be selected from the hospital population and interviewed in the same manner. Statistical analysis of data will be made with particular attention paid to the role of alcohol and tobacco, used either jointly or separately; individual analysis of beer, wine and whiskey will be included.

30. COMPARATIVE STUDY OF ALCOHOLISM AND CANCER OF THE HEAD AND NECK

Lowry, W. S., Queen's University of Belfast, Dept. of Oncology, *Belfast, Northern Ireland, United Kingdom*

One hundred patients with a diagnosis of head and neck cancer were investigated carefully for a history of alcoholism in the U.S.A. Most patients with cancer of the tongue, tonsil and oropharynx were alcoholics. About one half of the patients with supraglottic carcinoma were alcoholics. In the nasopharynx and true vocal cords, there was no association with heavy drinking. The study is now being extended to Ireland since the Irish ethnic group allegedly accounts for a considerable proportion of the American drinking problem. Initial results suggest that this may be exaggerated at least as far as the cancer problem is concerned.

31. TIME TRENDS IN ALCOHOL CONSUMPTION AND ALIMENTARY TRACT CANCER MORTALITY IN AUSTRALIA

McMichael, A. J., Commonwealth Scientific & Industrial Research Org., Div. of Human Nutrition, *Kintore Ave., Adelaide, S. Australia 5000, Australia*

Australia has a high consumption of alcoholic drinks, by international standards. Further, there has been considerable variation, both in amount and type of drink, during this century. By analysis of sex-age-specific time trends in cancer mortality in this century, in the light of consumption time trends for alcohol and cigarettes, the aetiological contribution of these two factors is being assessed for cancers of the oropharynx, oesophagus, colon, rectum and, particularly, the larynx. Specific attention is being paid to cohort analysis of the data. Case-control studies for cancers of the large bowel and the larynx are now being planned. The large Greek migrant population in Australia holds promise for case-control studies of cancer of the rectum, in view of the low incidence rates reported for Greece.

32. IDENTIFICATION OF POTENTIAL POPULATIONS FOR STUDIES

Mashberg, A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *Tremont Ave. & S. Centre St., East Orange, New Jersey,* 07019, United States of America

The VA Hospital will conduct the necessary activities to identify potential populations for studies of the relationship of alcohol consumption to the development of oral cancer.

33. FREQUENCY OF CANCER OF THE NASOPHARYNX IN YOUNG ARABS IN MOROCCO

Bompoint, J., Levy Lehbar, J. P., Centre Anticancereux du Maroco, *c/o Hopital Averroes, Casablanca, Morocco*

Following a study of the role of tobacco in 500 cases of larynx cancer seen at the Cancer Hospital of Casablanca, Morocco, which demonstrated a strong influence of smoking, particularly at an early age (Rev. Laryng. 97: 729-732, 1976), the characteristics of nasopharynx cancer, particularly in young age groups, are being studied.

34. SMOKING AND CHEWING HABITS IN RELATION TO HEALTH - A PROSPECTIVE STUDY IN BOMBAY

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A number of retrospective studies carried out in this country have demonstrated the association of smoking and chewing habits with oral and pharyngeal cancers. Laboratory and experimental studies on bidi smoke and betel quids have also served to establish this cause-effect relationship. To see whether the results obtained in retrospective studies are sustained in prospective studies in which large populations with known habits are followed for several years for the occurrence of cancer, a limited study of this nature has been in progress, following earlier pilot studies. About 7,000 white-collar workers and 3,500 blue-collar workers over the age of 35 have been followed up for varying periods since 1969. A preliminary analysis of the data on white collar workers is being undertaken.

35. EPIDEMIOLOGY OF SMOKING-RELATED DISEASES

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OBJECTIVES: The objectives of this project are to evaluate the risk associated with various smoking habits, including the type of cigarettes smoked, to identify the kinds of cigarettes that may be less carcinogenic to various body organs, and to measure the association between the smoking of various tobacco products and the development of myocardial infarction. This retrospective case-control study uses two sets of controls: One consisting of hospitalized patients and the second consisting of non-institutionalized persons residing in the same neighborhoods as the index cases.

MAJOR FINDINGS: The study continues to demonstrate a dose-response relationship between cigarette smoking and development of cancer of the larynx, lung, oral cavity, esophagus and bladder for both sexes. After adjusting for duration of the smoking habit, inhalation, and butt length, relative risks of developing lung or larynx cancer were consistently lower among long-term smokers of filtered ciagarettes (low tar) than among non-filtered cigarette smokers. For ex-smokers, the risk decreased with increased years of cessation. Risk of mouth cancer for pipe and cigar smokers, who inhaled much less than cigarette smokers, increased with the quantity smoked. Risk of mouth, larynx and esophagus cancer among smokers increased with the quantity of alcohol consumed. More extensive smoking and lower cessation rates were noted among lower socioeconomic groups, suggesting that these groups will bear an ever increasing proportion of the burden of tobacco-related diseases.

In accord with the literature, smoking among women is becoming increasingly more prevalent and, contrary to previous reports, persons smoking filtered cigarettes do not appear to significantly increase their levels of consumption once they have changed from a non-filter to a filter cigarette. In addition, when comparing case cohorts, one finds a significant increase in cigarette consumption among young people. Younger cancer patients generally have smoked more cigarettes than older patients. This is consistent with the observation that industrywide cigarette tar yields have been gradually decreasing over the years, and larger quantities are required to obtain the same risk levels. (Text Abridged.)

36. EPIDEMIOLOGY OF SMOKING-RELATED DISEASES

Wynder, E. L., Schottenfeld, D., Petrakis, N. L., Bahn, A. K., Bridgers, W., Wood, W., Kuller, L., Spritz, N., American Health Foundation Inc., Dept. of Epidemiology, *320 E. 43rd St., New York, New York,* 10017, United States of America

Although it has been well established that there is an association between smoking and certain diseases, not all smokers develop a tobacco-related disease. Variables such as length of cigarette smoked, depth of inhalation, tar output, carbon monoxide content, etc., along with demographic, occupational and other characteristics modify the exposure and risk for a cohort at a given lifetime exposure to cigarettes. The objectives of this case-control study are to identify individuals or groups at risk of tobacco-related diseases, to evaluate environmental, biological and smoking pattern characteristics of persons at high risk, and to analyze the relative effects of cigarette modification. Hospitalized patients who meet study criteria are interviewed by trained research interviewers in selected hospitals in New York, Philadelphia, Birmingham, Pittsburgh, Chicago and San Francisco. Cases are persons with a histologically confirmed diagnosis of cancer of the lung, bladder, pancreas, esophagus or oral cavity, or a first myocardial infarction; patients without a tobacco-related disease serve as controls. Two controls for each case, one from the hospital population and one from the residential area of the case, are matched by race, sex and age. Approximately 1,250 cases and 2,500 controls are interviewed each year.

37. EPIDEMIOLOGY OF THE LESS HARMFUL CIGARETTE

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By means of ongoing case-control studies, the investigation (1) monitors the use of cigarettes with differing levels of tar and nicotine by hospitalized patients, and (2) identifies the effects of smoking the 'less harmful cigarette' on the development of a wide variety of diseases. Analysis of 3,716 patients with histologically proven cancer of the lung (Kreyberg I and II), mouth, larynx, esophagus, or bladder and more than 18,000 control patients has been published (Cancer Res., 37:4608-22, 1977). A strong relationship between socioeconomic status and tobacco-related cancer is reflected in the smoking habits of different groups. Data from 1,934 white male and female patients with histologically verified cancer of the lung (Kreyberg I) and larynx cancer and matched controls have been analyzed (J. Natl. Cancer Inst., in press). Relative risks for developing either lung or larynx cancer were consistently lower among long-term smokers of filter cigarettes than for non-filtered cigarette smokers, irrespective of quantity smoked and after adjustment for duration of the smoking habit, inhalation and butt length. Risk of developing either cancer declined with years passed since ceasing to smoke. The changing smoking habits of women were studied in relation to the possible interaction between occupational health problems and cigarette smoking faced by an increasing proportion of the female population (Prev. Med., in press). It was found that more women are beginning to consume daily the same quantities of cigarettes as their male counterparts. More non-smokers are represented in the older than the younger age groups of women, supportive evidence of the national trend of increased smoking among young women. The profile of today's female smoker is that of a young, well-educated, social, employed, career-oriented person. Data continue to be collected in New York City and five other cities across the U.S. towards the goal of identifying risks of disease associated with smoking.

38. INCIDENCE OF SECOND SQUAMOUS CANCERS OF THE HEAD AND NECK IN SMOKERS AND THOSE WHO HAVE CEASED SMOKING

Moore, C. N., Flynn, M. B., Greenberg, R., University of Louisville, School of Medicine, Dept. of Surgery, *101 W. Chestnut, Louisville, Kentucky,* 40202, United States of America

The aim of the study is to compare equal groups of individuals who have been smokers and who have been cured of one squamous cancer of the head and neck (excluding skin) dividing them into two subgroups: (1) those who continue to smoke three years after the control of the first cancer; and (2) those who cease smoking with the discovery of their first cancer. The incidences of second cancer in the two groups can then be compared over a long period extending to 20 years or the lifetime of most patients.

39. GENETIC AND BIOMARKER STUDIES OF SMOKING-ASSOCIATED CANCERS

Lynch, H. T., Creighton University, School of Medicine, Dept. of Preventive Medicine & Public Health, *629 N. 27th St., Omaha, Nebraska,* 68131, United States of America

The primary aim of this proposal is to identify the role of genetic (host) factors which are contributory to the etiology of smoking-related cancer (carcinoma of the oral cavity, pharynx, larynx, respiratory tract, pancreas, and urinary bladder). A consecutive series of patients with the subject malignant neoplasms, who are undergoing treatment at oncology clinics at Creighton and the University of Nebraska Medical Center, will be studied. The patients will have their family histories meticulously scrutinized. Pedigrees will be constructed with attention given to cancer of all anatomic sites. A permutation test and segregation analysis will be used as statistical models for testing hypotheses relating to possible single gene inheritance. Families fulfilling these genetic criteria will be investigated in detail utilizing specific biomarker studies which will include skin biopsies for Kirsten murine sarcoma virus, recognitive immunity, and genetic linkage using standard serum and red cell markers. Environmental history, including cigarette smoking and alcohol consumption, in addition to characteristics of cancer, including age at onset, pathology, prognosis, and survival, will be incorporated into the model for the testing of factors which may influence gene penetrance and expression. These data will be computer-coded and subjected to comprehensive statistical genetic analyses. A cancer susceptibility index will then be developed.

40. EPIDEMIOLOGICAL MODELS FOR THE STUDY OF ENVIRONMENTAL CARCINOGENESIS

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OBJECTIVES: 1) To estimate the population attributable risk determined by several etiological factors for cancer of the urinary tract and other sites; 2) to study the mechanisms of interactions between different etiological agents in carcinogenesis.

APPROACH: The design is that of case-control studies. Cases of cancer of the urinary tract are male residents in the Province of Torino. They are contacted and interviewed in the three main hospital urological wards of the Province. Each case is sex- and age-matched with a hospital control from the same urological ward (excluding cancer at any site, cystitis and haematurias of unknown origin). Information is collected on smoking habits, coffee consumption, use of analgesics and artificial sweeteners and occupational history throughout life. A further control group is represented by a random sample of residents in the city of Torino. During 1980, 92 such controls were interviewed. Other sites to be investigated in a similar way are cancer of the larynx and cancer of the mouth.

PROGRESS: Data regarding occupational and smoking histories of the first 225 pairs (bladder cancer case-hospital control) have been analyzed. Age-standardized relative risks associated with tobacco smoke were 4.8 for all smokers and 2.5, 6.1 and 7.1 respectively for smokers of 1-9, 10-19 and 20 plus cigarettes/day. The relative risk associated with occupations known to have an etiological role in cancer of the urinary tract (lasting at least 6 months in any life period) was 1.8. Relative risks determined by cigarette smoke were also estimated separately in persons occupationally exposed and non-occupationally exposed. The comparison suggests a multiplicative effect.

41. SMOKING AND ALCOHOL CONSUMPTION IN SOME TYPES OF CANCER (CASES AND CONTROLS)

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OBJECTIVE: 1) To prove the hypothesis linking the habit of smoking and the ingestion of alcohol with oral and laryngeal cancers. 2) To determine the risks associated with light and dark tobaccos in relation to certain types of cancer (laryngeal, oral, pulmonary, and bladder). 3) To define the relationship between various smoking habits and cancer. For example, the relationship between reverse smoking (holding the lit end of the cigarette inside the mouth) and oral cancer.

APPROACH: This study will be based on the previous findings obtained by the cancer registry in affiliation with the Social Security. Those findings indicated a disquietingly high incidence of oral and laryngeal cancers in the population studied. This high incidence was offset by low rates of lung cancer.

METHOD: The project is designed to pair off one case and two controls for each type of cancer, that is cancer of the larynx, oral cancer, lung cancer and bladder cancer. One control is matched with the case for age, sex and occupation, whereas the other control is matched for age, sex, socioeconomic class and place of residence.

PROGRESS: To date, 249 cases have been selected, but they have not been matched with controls. In February 1979, a preliminary analysis was performed, and it was determined that a minimum of 60 cases and 120 controls should be obtained for each type of cancer.

The Cancer Registry of the Instituto de Seguros Sociales of Antioquia remains active. An analysis of data for the 10 year period (1968-1967) will soon be published.

42. A STUDY OF THE ETIOLOGY OF CANCER OF THE HEAD AND NECK IN THE REPUBLIC OF IRELAND

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This is a retrospective case-control study of cancers of the oral cavity, nose and paranasal sinuses, pharynx and larynx. The aim of the study is to explore differences between cases and controls in relation to tobacco and alcohol consumption, social conditions, occupation, and previous medical history. Clinical data, staging of tumors, histology and treatment given will also be recorded. Patients attending St. Luke's Hospital for the treatment of skin conditions are used as controls. Controls are matched with cases by age, sex and domicile.

43. CASE-CONTROL STUDY OF ETIOLOGICAL FACTORS IN HEAD AND NECK CANCER

Elwood, J. M., Jackson, S., Flores, A., Willan, A. R., Cancer Control Agency of British Columbia, Epidemiology Division, *2656 Heather St., Vancouver, British Columbia,* V5Z 3J3, Canada

The objective of the study is to evaluate the association of alcohol, tobacco and occupation to cancer of the head and neck, and to determine whether such exposures are independent or interactive. It is planned to interview all new patients with these tumors seen at the Cancer Control Agency of British Columbia (which includes about 90 percent of new cases in the province) over a 3 1/2 year period, to give a total of about 350 cases. The control group will consist of an age-and sex-matched group of patients with other tumors chosen on the basis of lack of association with the main exposures, for example breast and gynecological cancer in women, chronic lymphomas and multiple myeloma, and prostatic tumors in men. The interview will provide information on a lifetime occupational history and quantification of current and past tobacco and alcohol usage habits.

44. ALCOHOL, TOBACCO AND AGE FACTORS IN THE RELATIVE FREQUENCY OF CANCERS AMONG MALE NEGROES WITH AND WITHOUT LIVER CIRRHOSIS

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Because ethnic factors contribute to distinct distributions of many diseases in the United States and can frequently explain still other factors in their etiology, and because, further, a recent study yielded substantial data on white cancer patients with and without liver cirrhosis, there is a decided need for comparable data on Negroes. These data will facilitate valid racial comparisons in regard to tobacco and alcohol consumption, cancer sites and age disparities among males, with and without liver cirrhosis, and may delineate factors in cancer etiology which are specific to one race. Negro cases (with liver cirrhosis and cancer) and Negro controls (with cancer but not liver cirrhosis) from the 171 veterans' hospitals in the United States will be examined over a six year period. This research will endeavor to demonstrate the extent to which cirrhotics manifest significant excesses of specific digestive organ, oral cavity and pharyngeal cancers with regard to types and amounts of tobacco smoked and alcohol consumed. The probable roles of some occupational exposures in the pathogenesis of cancers in cirrhotics will also be assessed. Subsequent analyses will entail the comparison of data on Negroes with data, already published, on 286 white males with liver cirrhosis and cancer and on 374 white males with cancer only.

45. SYMPTOMATOLOGY AND RISK FACTORS OF CANCERS OF THE LARYNX AND OF THE HYPOPHARYNX

Raymond, L. M., Lehmann, W., Tuyns, A., Registre Genevois des Tumeurs, Centre de cytologie et de depistage du cancer, *55 Blv. de la Cluse, 1205 Geneva, Switzerland*

The study consists of 2 parts: 1) Analysis of the symptoms and the lead times as a function of diagnostical aspects (starting point of the lesion, clinical stage, etc.). 2) Case-control approach in order to evaluate the importance of the following factors: tobacco, alcohol and occupation.

The second part is being carried out in collaboration with Turin, Saragosse, Varese and Caen.

46. CANCER OF THE OROPHARYNX - A CASE-CONTROL STUDY

Sivayoham, S., National Cancer Registry, Dept. of Health Services, *385 Deans Rd., Colombo 10, Sri Lanka*

The data available from the Sri Lanka National Cancer Registry show that oropharyngeal neoplasms constitute 39% of all cancers in Sri Lanka. The age-adjusted rates, when compared with other cancer registries, are very high, if not the highest. For example, the age-adjusted rate for mouth cancers is 56.7 for males and 20.5 for females, many times higher than that provided by any other registry. The objective of the present epidemiological investigation is to study the association between possible risk factors, betel chewing, smoking, the consumption of alcoholic drinks, oral hygiene, socioeconomic factors, and oropharyngeal cancers in Sri Lanka. The cases will be drawn from the Cancer Institute, Maharagama, and the General Hospital, Colombo, and the control group from non-cancer inpatients of the General Hospital, Colombo.

47. LOCAL CAUSES IN THE ETIOLOGY OF HEAD AND NECK CANCER

Inal, E. C., Unver, S., Ankara Oncology Hospital, *Imrahor Caddesi, Incesu, Ankara, Turkey*

Local causes in the etiology of head and neck cancers (i.e., buccal mucosa, tongue, gingiva, floor of mouth, oropharynx, hypopharynx, tonsils, larynx and upper esophagus, excluding nasopharynx) are being studied. Information is sought on use of alcohol, tobacco, cleaning of teeth, kind of food taken, preferred foods, temperature at which food and drinks are taken, habit of biting the tongue or buccal mucosa and the habit of taking foreign bodies in the mouth (some drugs are retained in the mouth for a long time).

48. AMERICAN HEALTH FOUNDATION EPIDEMIOLOGICAL STUDIES

Spritz, N., Wynder, E. L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Medical Service, *1st Ave. at E. 24th St., New York, New York,* 10010, United States of America

Tobacco-related cancers and myocardial infarction continue to constitute a major source of death and disability in the U.S. (deaths and morbidity which largely are preventable because of their association to tobacco usage). Collection of data on smoking habits, demographic characteristics, alcohol consumption, occupational and medical histories of patients with tobacco-related diseases and matched controls continues. Annually, 300 lung, esophagus, and bladder cancer patients plus 300 first episode myocardial infarction and 150 pancreatic cancer patients will be interviewed. Results indicate that the risk of developing these diseases increases with quantity smoked, duration of the habit and, for lung and larynx cancer, non-filter cigarette smoking. Risk of mouth, larynx and esophagus cancer among smokers increases with quantity of alcohol consumed. Increased smoking and low cessation rates are noted among lower socioeconomic groups suggesting that these groups will bear an ever increasing proportion of the burden of tobacco-related diseases.

Collection of data (on demographic characteristics, diet and lifestyle habits) in patients with gastrointestinal tract cancer and control patients continues. To date we have 799 gastrointestinal tract cancer cases and an equal number of controls. Fifty percent of the cases have primary colon cancer, 18% have primary rectal cancer, 16% have primary gastric cancer, and 12% have intestinal polyps.

A preliminary analysis of demographic variables and dietary factors has been performed, and a paper is in preparation.

D. ROLE OF DIET AND NUTRITION

49. SOCIAL EPIDEMIOLOGY AND CONTROL OF CANCER

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We request renewal of support of this program of research in Social Epidemiology and Control of Cancer. In the area of epidemiology, we would complete analyses on data already collected in the following areas: dietary vitamins, meats, fiber, cruciferous vegetables and other aspects of diet in cancer of the esophagus and larynx, to be studied in cases and controls from Roswell Park Memorial Institute (RPMI); reliability of diet interviewing, based on spouse interviews, diet diaries and 24-hour recall of diet in our Western New York Study; the interrelationships of herpes simplex virus 2, numbers of sex partners and other factors in cancer of the cervix in Los Angeles blacks and Chicanos; epidemiology of melanoma in 450 cases and 450 controls from RPMI. In addition, we wish to continue our ongoing data collection for the epidemiologic study of: cancer of the mouth, esophagus, stomach, larynx, colon, rectum, lung and bladder being carried out among all pathologically confirmed cases in Monroe, Niagara and Erie Counties and controls residing in the neighborhoods of cases; cancer of the testis and penis patients residing in New York State, as compared with controls residing in their neighborhoods; the interaction of oral contraceptives with other risk factors in the epidemiology of breast cancer; a prospective study of cancer among approximately 200,000 physicians and nurses in New York State, emphasizing diet. Throughout the period of study, we would carry on analyses of most of the above-named cancers for human genetics relationships.

Because many measures that can prevent or control cancer devolve from the epidemiology of those diseases and can involve changes in the human behavior, we are interested in the social and behavioral factors associated with cancer prevention and control. Thus, we wish to complete data collection in our study of the efficacy of breast self-examination (BSE) by comparing the proportion of breast cancer patients with advanced and early lesions who have practiced BSE. We also plan a study of lower-middle, upper-middle and rural residents of Erie County, building upon our earlier inquiry on blacks, to ascertain their knowledge of cancer.

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50. MODIFYING EFFECT OF DIET ON UPPER ALIMENTARY TRACT CANCER IN PERSONS WHO CHEW AND SMOKE TOBACCO

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Tobacco chewing and smoking habits carry a high risk for cancers of the upper alimentary tract, yet not all those who chew or smoke heavily contract the disease. This indicates a role for other factors which may have a modifying effect on these risks. Preliminary study of existing records of a Bombay population indicated a reduction in oral cancer risk in persons with tobacco chewing and smoking habits who ate eggs, meat or fish (Ind. J. Cancer, 13: 156-160, 1976). A pilot study was carried out to standardize the methods for collection of dietary information such as the type and quantity of Indian spices, consumption of vegetables, pulse and fat in addition to eggs, meat and fish. Data on habits and diet have been collected on cases and 167 controls during the current year. It is proposed to continue collection of data during 1980 following which the material will be analyzed.

51. TRI-COUNTY STUDY OF CANCER OF THE MOUTH, ESOPHAGUS, LARYNX, STOMACH, COLON, RECTUM, LUNG AND BLADDER

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PROJECT OBJECTIVES: (1) To study the epidemiology of cancer of the gastrointestinal tract, lung and bladder. (2) To study the possible relationship between dietary factors and cancer at the aforementioned sites.

PLAN AND METHODS: We are attempting to interview all patients in Erie, Niagara and Monroe Counties who develop histologically confirmed neoplasms of the gastrointestinal tract, lung and bladder. Nine patients at the Veterans Administration Medical Center have been entered in the study since the last report.

The major emphasis in the interview is on dietary habits. Questions are asked about time and frequency of eating meals, types and amounts of food eaten, and methods of food storage and preparation. In addition, questions are asked about alcohol consumption and use of tobacco, and data on age, occupation and marital status are gathered.

In addition to interviewing cases, we are also interviewing neighborhood controls matched on age (plus or minus 5) and sex.

FINDINGS, RESULTS: We have not undertaken any definitive analyses of our data since our numbers at various sites are still too small. We have, however, completed a methodological study based on this series which examines degree of agreement between case-spouse and control-spouse pairs with regard to food frequency. We presented our findings on this at the meeting of the Society for Epidemiologic Research on June 14, 1979.

52. DESCRIPTIVE AND ANALYTICAL EPIDEMIOLOGY OF NASOPHARYNGEAL CARCINOMA IN HONG KONG, SINGAPORE AND TUNIS

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OBJECTIVES: To determine the incidence and risk factors of nasopharyngeal carcinoma (NPC).

APPROACH: The following studies of environmental factors in NPC aetiology have been analyzed: NPC case-control studies in Hong Kong.

PROGRESS: 1. The case-control study in Hong Kong was terminated in 1977 and showed that feeding salted fish during weaning was more common in NPC families than in controls. The NPC patients also tended to be on a somewhat lower socioeconomic level than the controls. See article: 'Environmental factors in the etiology of nasopharyngeal carcinoma: Report on a case-control study in Hong Kong' by A. Geser, N. Charnay, N.E. Day, H.C. Ho and G. de The. in 'Nasopharyngeal Carcinoma - Etiology and Control', G. de The and Y. Ito, eds. IARC Scientific Publications No. 20, 1978. 2. The analysis of data from the study in Hong Kong showed that diseases of ear and nose increase the risk of NPC. 3. The anthropological study of young NPC cases undertaken in Hong Kong indicated that during early childhood, the NPC patients had been living on poor diet, deficient in vitamin C, and that their consumption of salted fish had been as high as is usual among children in Hong Kong. See article: 'Environmental backgrounds of young Chinese nasopharyngeal carcinoma patients' by E.N. Anderson, Jr., M.L. Anderson and H.C. Ho. in: 'Nasopharyngeal Carcinoma - Etiology and Control', G. de The and Y. Ito, eds. IARC Scientific Publications No.20, 1978.

53. ETIOLOGIC FACTORS INVOLVED IN THE INCREASED INCIDENCE OF ORAL CANCER IN GOA REGION

Dias, F., Shirodkar, S. R., Vaidya, S. G., Harinath, B. C., G.M. Hospital & Research Inst., Laboratories of Biochemistry & Immunology, *E. Borges Rd., Dona Paula, Ilhas, Goa 403004, India*

Incidence of cancer of the oral cavity is observed to be higher than that of any other cancer type in this region. A study will be made to determine etiological factors for the increased incidence of oral cancer in the Goa region. Data on nutritional status, dietary history, occupation, and economic status will be collected. In addition, saliva and serum will be analyzed for nitrites, nitrosamines and antibodies to viral antigens to establish if there is any dietary or viral association with oral cancer in this region.

54. EPIDEMIOLOGY OF ORAL CANCER

Fischman, S. L., Graham, S., Kaufman, S., Lore, J., Shedd, D., Martinez, I., State University of New York, Health Science Center at Buffalo, School of Dentistry, Dept. of Oral Medicine, *3435 Main St., Buffalo, New York,* 14214, United States of America

A case-control study of the various nutritional and dietary factors common to patients with cancer of the oral cavity is in progress. Data on oral hygiene, use of dental prostheses, smoking, and alcohol consumption are also being obtained. Both self-administered questionnaires and interviews are used. For interim results see J. Nat. Cancer Inst. 59 (6): 1611-18, 1977.

55. ENVIRONMENTAL CARCINOGENESIS

Wynder, E. L., Hoffmann, D., Hecht, S. S., Williams, G. M., Silverman, J. M., Reddy, B. S., Hill, P. B., McCoy, G. D., American Health Foundation Inc., *320 E. 43rd St., New York, New York,* 10017, United States of America

This program project grant supports a number of studies related to environmental carcinogenesis. These studies are: 1. Epidemiology of gastrointestinal cancers - U.S. and Yugoslavia (E.L. Wynder). 2. Metabolic activation of 5-methylchrysene (D. Hoffmann, S.S. Hecht). 3. Metabolic epidemiology of large bowel cancer (B.S. Reddy). 4. Metabolic epidemiology in breast cancer (P.B. Hill). 5. The role of nutritional deficiency and alcohol in the etiology of head and neck cancer (G.D. McCoy). 6. Cell analysis of neoplastic development in the rat liver (G.M. Williams). 7. Epidemiologic studies of shipyard welders (J.M. Stellman).

E. SIGNIFICANCE OF ORAL PRECANCEROUS LESIONS

56. ETIOLOGY AND PREVENTION OF ORAL LEUKOPLAKIAS AND THEIR MALIGNANT TRANSFORMATION

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Oral leukoplakia is a well-known precancerous condition. On this assumption the aim of the present study has been to analyze prospectively the aetiology and pathogenesis of oral leukoplakias as well as the aetiology and pathogenesis of carcinomas developing in such leukoplakias. In this context availability of means of early diagnosis of oral carcinoma is important. By October 1978 the study comprised 750 persons who had all had a biopsy taken at the first examination. Follow-up biopsies have been performed in case of morphological changes of the lesions. Over the years the annual follow-up for each year has covered 93.6% of the persons with only small variations from one year to another. The influence of abstinence from tobacco upon the so-called candidal leukoplakia is also being studied.

57. LONGITUDINAL STUDIES IN ORAL LEUKOPLAKIA

Banoczy, J., Sugar, L., Csiba, A., Albrecht, M., Semmelweis Orvostudomanyi Egyetem, Conservative Dentistry Clinic, *Mikszath Kalman ter 5, 1088 Budapest VIII, Hungary*

Six hundred and seventy patients (670) with oral leukoplakia have been under continuous control over a period from 1 to 30 years, with a mean observation period of 9.8 years. The objectives studied are: the frequency of malignant transformation, the distribution according to age, sex, localization and smoking habits, possible etiological factors and the conditions favoring malignant transformation. In the histological material of the same leukoplakia patients the frequency of histological dysplasia and cancer as well as the ultrastructural characteristics by transmission and scanning electron microscopy are studied in correlation with the clinical types of leukoplakia. The patients with oral leukoplakia come from the Clinic of Maxillo-Facial Surgery and Clinic of Conservative Dentistry, Semmelweis Medical University, Budapest. Some of the results have been published. (J. Maxillofac. Surg. 5(1), 69-75, 1977, J. Oral Path. 1979).

58. BIOCHEMICAL, IMMUNOLOGICAL AND EPIDEMIOLOGIC STUDY OF LEUKOPLAKIA CASES AND THEIR TEN-YEAR FOLLOW-UP

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In the health camps organized by the Goa Cancer Society, about 10% of the examinees have leukoplakia. About 100 such cases will be followed up for the next ten years for development of malignancy, if any. Serum and saliva will be analyzed for certain biochemical (amylase, etc.) and immunological (CEA, etc.) markers at yearly intervals and sera will be stored for further follow-up.

59. RISK OF WHOLE BODY MALIGNANCY IN PATIENTS WITH ORAL LEUKOPLAKIA

Roed Petersen, B., Moller Jensen, O., Finseninstitutet, Danish Cancer Registry, *Strandboulevarden 49, DK2100 Copenhagen, Denmark*

OBJECTIVE: To establish relative risks of malignancy anywhere in the body in patients with oral leukoplakia.

APPROACH: Data linkage is established between a registry of oral leukoplakia patients comprising 650 patients in long-time follow-up and the files of the Danish Cancer Registry. The relative risk will be based on national figures.

PROGRESS: The project is to be initiated by January 1, 1981.

60. FOLLOW-UP OF PREMALIGNANT LESIONS OF ORAL CAVITY AND OROPHARYNX

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From 1967 to 1972, a multi-purpose study of carcinoma of the oral cavity and oropharynx was carried out in this centre. In this study 724 cases with premalignant lesions (mostly leukoplakia) were registered. The records of the cases are available, and these are being reexamined and the cases followed up.

61. AN INVESTIGATION INTO THE SO-CALLED PREMALIGNANT LESIONS OF THE ORAL CAVITY

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The object of the study is to determine the prevalence, the anatomical distribution, the histopathology, the ultrastructure and histochemistry of the so-called premalignant oral lesions (leukoplakias) among different population groups in Cape province (Bantu, colored, white and Asian) paying due regard to habits, social circumstances and geographical distribution. Furthermore, a similar demographic study is being carried out on oral squamous carcinomas among the same people to make comparisons between the premalignant and malignant lesions possible. In addition all other oral mucosal lesions detected during the survey are recorded and their distribution plotted. Specific investigations are undertaken into the etiology of some, especially the atrophic lesions and lesions caused by viral infections.

62. DEVELOPMENT OF AN ORAL LEUKOPLAKIA PRONENESS PROFILE

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This study was designed to determine the feasibility of developing an oral leukoplakia-proneness profile with the ultimate goal of identifying those factors associated with an increased risk of developing oral leukoplakia (and presumably subsequent squamous cell carcinoma). Ten subjects with leukoplakia were compared according to several parameters with a like number of control patients. Data were gathered by way of physical examination to include general nutritional appearance, height, weight, ponderal index, upper arm circumference, and triceps skin fold thickness; oral examination; social and medical history; tobacco, alcohol, and drug experience; a dietary questionnaire (Dietronics, Inc.,); A Cornell Medical Health Index Questionnaire; biopsy and cytology specimens; routine automated fasting blood chemistries (SMAC-20); non-automated serum studies for carotene, ascorbic acid, folate, iron-binding capacity, vitamin A, vitamin B-12, thiamine, riboflavin, niacin, pyridoxine, chromium, cobalt, copper, zinc, manganese and selenium; routine hemoglobin studies (Coulter); routine urinalysis and urine quantitations for creatinine, N-methylnicotinamide, thiamine and riboflavin; enumeration of circulating T-lymphocytes by the rosette method; and circulating lymphocyte stimulation testing with PHA, conA, LPS, herpes virus I antigen and Candida albicans antigen. Leukoplakia patients tended to show: 1) higher incidence of tobacco and alcohol use; 2) underweight by the various body weight status indexes; 3) 'poorer' dietary patterns with respect to protein ratio and vitamin intake (particularly vitamin A); and 4) lower levels of serum albumin, folate, and hemoglobin. We will continue this study with a change in patient population to include patients with oral squamous cell carcinoma and epithelial dysplasia.

63. A LONGITUDINAL AND CROSS-SECTIONAL STUDY OF ORAL HEALTH IN HEALTHY VETERANS

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PROJECT OBJECTIVES: The specific aim of this investigation is to determine the incidence, distribution, changes, and interrelationships of oral variables used to indicate oral health. Information is obtained during periodic examination, performed at three-year intervals, of more that 1,200 DLS participants.

PLAN: This oro-facial study includes six series of examinations or procedures: 1) Interim health history; 2) oro-facial examinations; 3) tests of masticatory function and survey of dietary habits; 4) biochemical analyses of stimulated whole and parotid saliva; 5) intra-oral and cephalometric radiographs, standardized photographs and study models of the teeth; 6) oral cytological examination.

METHOD: These comprehensive oral examinations permit a detailed description and analysis of the effect of age on oral tissues and functions and elucidate the natural history of oral diseases.

CLINICAL RELATIONSHIP: The DLS determined the prevalence of oral leukoplakic lesions in 'nonsmokers' and persons who smoked either cigarettes, cigars, pipes or cigars plus a pipe. The data indicated that the prevalence of oral leukoplakia was associated with smoking and differed according to the type of product used. Individuals smoking a 'pipe' or 'cigars plus a pipe' exhibited the highest overall prevalence rate, especially for the palate.

Changes in masticatory ability with age were primarily due to the loss of natural dentition with subsequent replacement by a removable prosthesis. Approximately 1,200 men were classified by denture status. A plot of masticatory performance vs. mean perceived chewing ease, for thirteen food items, separated out the dentition groups by degree of impairment. A clustering of the dentition groups occurred. The robustness of the clusters suggested that characteristic food selection patterns can be formulated according to degree of impairment.

64. PREVALENCE OF ACTINIC CHEILITIS AMONG THE RURAL POPULATION IN THE SOUTH OF CHILE

Martinez, B., Ramirez, T., PLAPO, *Jose Miguel de la Barra 475, Casilla 1903 - Correo Central, Santiago, Chile*

OBJECTIVES: To establish the prevalence of actinic cheilitis in the farming population during the summer months and compare it to the prevalence during the winter. To determine the relationship of this lesion with hypermelanogenesis of the cheeks, the possible co-existence of the two lesions and/or the sequence of appearance of the lesions. To establish the relationship of hyperpigmentation with some factors such as ingestion of wine or apple alcohol (apple 'chicha'). At the same time, the prevalence of other lesions of the oral mucosa (especially precancerous lesions: leukoplasia, erythroplasia), lichen planus and recurrent oral aphtae will be determined in the same population.

APPROACH: Odontology students in their last semesters of study are provided with basic knowledge regarding the mentioned lesions followed by training specific to the region under study. The students are assigned to perform a house-to-house survey of all inhabitants over 15 years of age on certain islands in the Chiloe Archipelago. The islands have been selected based on ethnic, social, cultural and economic considerations.

PROGRESS: To date 860 surveys have been completed. They are being processed at the Computer Center of the School of Engineering, University of Chile. The survey questionnaires are based on a World Health Organization questionnaire that has been modified for use specifically within this region.

65. STUDIES OF ORAL FOCAL EPITHELIAL HYPERPLASIA

Praetorius, F., Fejerskov, O. E., Guertler, H., Gessain, R., Bearman, J. E., Kobenhavns Tandlaegehojskole, Dept. of Oral Pathology, *Universitetsparken 4, DK2100 Copenhagen OE, Denmark*

Oral focal epithelial hyperplasia is widespread among Eskimos and Amerindians, but rare among Caucasians (Europides). In Greenlanders there seems to be a direct relationship between the prevalence found and the degree of mixture of the population with Caucasians. This may be due to an influence of a genetic factor, and serological studies are, therefore, performed. Histology and electron microscopy seem to indicate a viral etiology of the disease; the size and morphology of the viruslike particles correspond to what has been described in verruca, condylomata, and in oral papillomatosis in dogs and rabbits. Pilot studies employing the immunofluorescence technique have shown that patients with focal epithelial hyperplasia produce antibodies against an antigen in the affected cells. It is likely that the disease is contagious. Epidemiological studies have been performed on 3,500 persons in Greenland and on population groups of Greenlanders and Danes in Denmark. Follow-up studies are undertaken in Greenland. Electronic data analysis of the collected material is performed in collaboration with J.E. Bearman. Blood group type studies are done on saliva samples from the same persons and are performed in collaboration with Dr. H. Guertler, Copenhagen. Family studies are carried out in collaboration with Dr. R. Gessain, Paris, who is in possession of records of the entire Eskimo population of the east coast of Greenland, dating back to about 1820. Biopsies from Greenland are studied histologically and ultrastructurally; immunofluorescence studies are also carried out. The electron microscopic studies are performed in collaboration with Dr. O. Fejerskov, Arhus, Denmark. Tissue culture studies are also performed.

66. MALIGNANT POTENTIAL OF ORAL LICHEN PLANUS

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The objective of this study is to obtain information on the potential for malignant transformation of oral lichen planus lesions over a 15-year period. Seven hundred (700) patients with histologically verified oral lichen planus are being followed. The patients are asked about past and present oral symptoms and smoking habits. The location and type of oral lichen planus lesions are registered and photographed. After the first examination the patients are seen once a year, except those with epithelial dysplasias who are seen every three months. At the follow-up examinations all changes in the lesions are recorded, photographed and, if necessary, biopsied. So far, five patients have been found with a simultaneous occurrence of lichen planus and erythroplakia. The influence of smoking on the lesions will be studied.

67. EPIDEMIOLOGY OF ORAL CANCER

Roy Chowdhury, J., Chakrabarti, R. N., Saha, I., Dutta, H., Sha, S. P., Roy, N. N., Patra, G. H., Das Gupta, P. S., Ghosh, K., Sarkhel, T., Ghosh, A., Sikdar, S., Chittaranjan National Cancer Research Centre, Dept. of Epidemiology/Pathology, *37 S.P. Mukherjee Rd., Calcutta, 700026, West Bengal, India*

Oral cancer, the commonest form of cancer in Indian men, is often preceded by some white precancerous lesions. The objectives of the present study are to establish the frequency of both oral cancer and precancerous lesions in urban and rural populations in West Bengal and the frequency of malignant transformation of white precancerous lesions and to examine the distribution by age, sex, localization, tobacco chewing and smoking habits. Other possible etiological factors, such as nutritional and dietary factors, oral hygiene, use of dental prosthesis and alcohol consumption, are also being investigated.

68. AN INVESTIGATION INTO ORAL CANCER AND ORAL PRECANCEROUS LESIONS IN INDIAN RURAL POPULATIONS IN RELATION TO TOBACCO HABITS

Mehta, F. S., Pindborg, J. J., Hamner, J. E., Daftary, D. K., Gupta, P. C., Tata Inst. of Fundamental Research, Basic Dental Research Unit, *Homi Bhabha Rd., Bombay 400005, Maharashtra, India*

Oral cancer is one of the most common forms of cancer in India. There is a strong belief that such cancer may be preceded by certain white lesions in the oral cavity, which are thus termed precancerous. It is known, mostly through hospital-based studies, that oral tobacco habits are associated with oral cancer and precancerous conditions. The main objectives of the present study are to (1) investigate the degree of association between tobacco habits, oral cancer and precancerous conditions, and (2) elucidate the natural history of oral precancerous conditions from clinical and histological viewpoints. The study design is prospective in nature. In a first survey in 1967-1968, in five districts in different parts of India where different tobacco habits prevail, 50,000 individuals were interviewed about their tobacco habits and examined for the presence of oral precancerous conditions. Since 1969 these individuals have been followed up annually, clinically, histologically, and cytologically, for change of habits and development of oral precancerous conditions. Follow-up surveys comprising a period of 10 years have been completed. A comprehensive report on the follow-up study is now under preparation.

69. EPIDEMIOLOGICAL AND CYTOPATHOLOGICAL STUDY OF NATAL BETHEL-CHEWING INDIANS WITH SPECIAL REFERENCE TO SUBMUCOUS FIBROSIS

Randeria, J. D., University of Durban Westville, Cancer Research Inst., *Private Bag X54001, Durban 4000, Natal, South Africa*

Oral submucous fibrosis has been reported almost exclusively among Indians, especially betel/tobacco chewers. The lesion is believed to be precancerous. Qualitative and quantitative studies are being made of the Papanicolau-stained buccal smears. Epidemiological data are collected in a questionnaire at interview. Partial results of the study have been published (Proc. VI Perugia Quadrennial International Conference on Cancer. Perguia, June 1977).

70. NATIONAL REGISTRY OF ORAL PRECANCEROUS CONDITIONS

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Preliminary studies indicate that, as in the case of oral carcinoma, there is a predominance of Indian patients (72%) with oral precancerous conditions. The findings are presented in detail in the Med. J. Malaysia 33, 1979. Work continues on submucous fibrosis which may be an Asian version of the sideropenic dysphagia seen in Caucasians. Biochemical studies are being carried out.

F. ROLE OF OCCUPATIONAL, ENVIRONMENTAL, AND OTHER FACTORS

71. CASE-CONTROL STUDY ON THE OCCUPATIONAL AETIOLOGY OF PARANASAL SINUS CANCER

Hernberg, S. G., Linderborg, H. N., Tola, S. A., Inst. of Occupational Health, Dept. of Epidemiology & Biometry, *Haartmaninkatu 1, SF00290 Helsinki 29, Finland*

This is a pilot study in which all 52 cases of cancer of the paranasal sinuses recorded during 1970-1973 and their age-matched controls have been identified in the Finnish Cancer Registry. After confirming the diagnoses in the hospitals, questionnaires concerning the occupational histories will be sent to the patients or their relatives. The present study will be followed by an Inter-Scandinavian prospective case-control study.

72. THE ROLE OF OCCUPATION IN THE ETIOLOGY OF LARYNGEAL CARCINOMA

Kelsey, J. L., Zagraniski, R., Stolwijk, J. A., Fischer, D. B., Kirchner, J. A., Meigs, J. W., Yale University, School of Medicine, Dept. of Epidemiology & Public Health, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

This is a case-control study of white male laryngeal cancer cases seen in the Yale-New Haven Hospital Head and Neck Clinic, newly diagnosed and histologically confirmed between 1977 and 1980. For each case, several white male general surgery admissions (excluding specific diagnoses) who live in the same county and are in the same age stratum as the case will be identified using hospital records. These persons will be briefly interviewed on the telephone to obtain two persons who match the case on smoking. The controls who meet the smoking requirement and who agree to participate will be interviewed in person by a trained interviewer. It is expected that 100-125 cases and 200-250 controls will be evaluated in the study. The subjects will be personally interviewed, preferably in the hospital, but because many will be cases previously seen in the hospital up to 300 may be interviewed in their homes. The risk factors of primary interest are occupational exposures; smoking habits and alcohol consumption will be taken into account in the analysis.

73. WOOD WORKERS AND CANCER

Esping, B., Axelson, O., University of Linkoping, University Hospital, Dept. of Occupational Medicine, *58185 Linkoping, Sweden*

An excessive incidence of cancer of the nose has been found among wood workers. There are also some indications of an excessive incidence of malignancies elsewhere, but few systematic studies are available. Malignancies of other sites, particularly of the respiratory system, will, therefore, be studied to examine the possible relationship to wood dust exposure. Both the case-control and the cohort approach will be applied in two studies. Various types of wood will be studied with regard to their potential cancer producing properties.

74. OCCUPATIONAL, ATMOSPHERIC AND DIETARY FACTORS AND HABITS ASSOCIATED WITH EPIDERMOID CARCINOMA OF THE BUCCAL CAVITY IN CHILE

Inzunza Hernandez, O., Cabezas Soriano, J., Majlis Moisseff, G., Hospital Jose Joaquin Aguirre, Asignatura de Fisiopatologia, *Av. Santos Dumont 999, Santiago, Chile*

OBJECTIVE: Information is available in the world literature on factors associated with buccal cancer, such as alcohol and tobacco consumption, diet and other habits. Given the ethnic, geographic, cultural and social differences between Chile and the countries producing this information, we propose to study the factors associated with buccal cancer in this country. The final objective is to apply the information obtained to the diagnosis of a population at high risk of developing buccal cancer and to implement in those persons preventive methods and early diagnosis of the neoplasia. We believe that based upon this analysis we will be able to detect mutagens for further study.

METHODS: 1) Analysis of morbidity and mortality statistics for buccal cancer throughout the country, studying the extent of the sample, distribution by anatomic site, distribution by geographic site, etc. 2) Analysis of the type of diagnosis, e.g., clinical, radiographic, histopathologic, type of pathology, degree of extension of the lesion, etc. 3) Using records of various treatment centers, compile a list of patients who are alive, who have epidermoid carcinoma of the buccal cavity or premalignant or potentially cancerous lesions. 4) Selection of a control group, two controls per cancer patient, comprised of individuals with the following similar characteristics: race, age, level of education, place of residence, occupation. 5) Interview of patients and controls to include: time of development of the lesion, prior diseases, teething, family history, occupation, place of residence, diet, habits, etc. 6) Tabulation and discussion of results.

PROGRESS: We have completed steps 1 and 2 and we are currently compiling a list of patients with epidermoid carcinoma of the buccal cavity.

75. ETIOLOGICAL FACTORS IN CANCER OF UPPER RESPIRATORY AND DIGESTIVE TRACTS

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Four main groups of neoplasms (oral cavity, oropharynx, larynx and hypopharynx) are being analyzed. A comparative study is carried out with special reference to occupation, dental status, smoking and drinking habits, precancerous lesions, sex and age. These data will be compared for the four groups and for ENT Department outpatients without evidence of neoplasm.

76. SHIPYARD ASBESTOS DISEASE - MORTALITY EXPERIENCE

Selikoff, I. J., Churg, J., Hammond, E. C., Anderson, H. A., Suzuki, Y., City University of New York, Mount Sinai School of Medicine, School of Medicine, Dept. of Community Medicine, *1 Gustave L. Levy Pl., New York, New York*, 10029, United States of America

We are investigating the mortality experience of shipyard workers at a major coast shipyard, to ascertain whether their asbestos exposure will be associated with increased cancer mortality. A previous field survey of 1,000 current employees in the yard (Groton, Connecticut) showed a very high incidence of asbestosis in chest films, establishing that asbestos exposure had been common in the past.

One thousand nine hundred and sixty men were employed in the yard on January 1, 1967, for at least ten years. By December 31, 1979, 340 were known to be deceased (17%) and 1,500 (76%) were known to be alive. Of these 830 (42%) were still employed in the shipyard. One hundred and twenty remained to be traced (6%). We expect to trace well over 95% of the cohort and will then analyze the mortality experience of the group, comparing expected deaths, based upon National Center for Health Statistics data for Connecticut and for the U.S. as a whole, with the differential experience of the various trades in the cohort (pipe fitters, boilermakers, painters, carpenters, guards, foundry workers, electricians, machinists, etc.). We are also exploring the mortality experience of two additional cohorts in the same way; a ship repair yard in Baltimore, Maryland, and a new surface ship construction yard in Quincy, Massachusetts (the Connecticut yard constructs and repairs submarines). In each of the latter two, more than 2,000 workers comprise the cohorts.

It will be of interest to compare the mortality experience with that of other asbestos-exposed workers (insulators, factory workers, miners and millers), with special reference to total mortality, lung cancer, pleural mesothelioma, peritoneal mesothelioma, gastrointestinal cancer, oropharyngeal and laryngeal cancer, renal cancer and asbestosis. The statistical analysis will utilize both the death certificate enumeration and that following ascertainment, in comparing expected deaths with those observed.

77. ENVIRONMENTAL RISK FACTORS FOR NASOPHARYNGEAL CARCINOMA IN MALAYSIA

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The study aims to clarify evidence for an association between poorer socio-economic environments and nasopharyngeal carcinoma (NPC), and test the hypotheses that inhaled carcinogens in certain occupational settings and exposure to Cantonese salted fish are high risk factors for this cancer. The individual environments of 100 Chinese and 25 non-Chinese patients with NPC will be compared in order to identify particular patient-environment interactions that may play a part in the etiology of NPC. Relative risk will be computed using 125 controls sampled from the general population. The time and space dimensions of self-specific environments for family members will be established using daily activity patterns spread over one week. Structured and non-structured interviewing techniques will be employed. Field work will be carried out during the first year of the 24 month study in the State of Selangor, Malaysia, and data processing and analysis during the second year in Hawaii.

78. EPIDEMIOLOGIC STUDIES OF CANCER IN ALASKAN NATIVES

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OBJECTIVES: To study the incidence of cancer in Alaskan natives from 1974 onward and the mortality from cancer in Alaskan natives from 1960 to the present; to investigate several striking familial aggregations of cancer in Alaskan natives, particularly nasopharyngeal cancer and hepatocellular carcinoma; and to search for environmental determinants of nasopharyngeal cancer, with particular emphasis on the presence of nitrosamines in Alaskan preserved fish.

METHODS EMPLOYED: Newly diagnosed cancers and cancer deaths among Alaskan natives will be ascertained through the facilities of the Public Health Service Hospitals in which virtually all Alaskan natives receive their health care. The data will be collected in a format compatible with the SEER Registries to permit comparison with other U.S. populations. Cancer-prone families will be studied in collaboration with professionals from the Family Studies Unit of NCI's Environmental Epidemiology Branch, utilizing clinical and laboratory protocols tailored to the malignancies to be evaluated. This will include hepatitis B and Epstein-Barr virus assays, immunologic and genetic tests, and other serologic markers aimed at uncovering mechanisms of disease susceptibility. A case-control study of nasopharyngeal cancer is planned, which will focus on dietary exposures of possible etiologic interest. Samples of suspect native food items will be assayed for the presence of nitrosamines.

MAJOR FINDINGS: Since the project has only been under way for four months, there are no preliminary findings to report. Necessary personnel have been hired, a SEER-compatible abstract form designed, population estimates for the period of study developed, and the case-control study interview instrument is in the design stages. An agreement has been reached with the Eppley Institute in Omaha to conduct the nitrosamine studies.

SIGNIFICANCE TO BIOMEDICAL RESEARCH AND THE PROGRAM OF THE INSTITUTE: The projects in this proposal are directed toward investigating the unusual patterns of cancer in the culturally and geographically unique population that Alaskan natives represent and identifying risk factors for these cancers.

PROPOSED COURSE: This study is intended to cover a two-year period. The collection of morbidity and mortaligy data will be initiated in the first year. (Text Abridged.)

79. NASOPHARYNGEAL CARCINOMA

Krueger, G., Ablashi, D. V., Sesterhenn, K., Pearson, G., Bedoya, V. A., Wustrow, J., Universitat zu Koln, Immunopathology Section, *Joseph Stelzmann Str. 9, 5000 Cologne 41, Federal Republic of Germany*

The objective of this study is to correlate the incidence of various types of nasopharyngeal carcinoma with geographical distribution, anti-EBV titers, distribution of lymphocytic types (T and B) in blood and tumour tissue, the course of the disease and prognosis. The investigations will be an extension of our earlier studies (G. Konorza et al.: Distribution of T- and B-cells and of Immunoglobulin-producing Cells in Tumor Tissue of Patients with Nasopharyngeal Carcinoma. J. Cancer Res. Clin. Oncol. 93: 195, 1979).

80. EPIDEMIOLOGICAL STUDY OF INCIDENCE, MORBIDITY & NATURAL HISTORY OF SOME TYPES OF CANCER, BY RELIGIOUS GROUP, IN THE BOMBAY AREA POPULATION

Jussawalla, D. J., Jain, D. K., Yeole, B. B., Natekar, M. V., Rajagopalan, T. R., Tata Memorial Hospital, Dept. of Surgery & Chemotherapy, *Dr. Ernest Borges Marg, Parel, Bombay 400012, Maharashtra, India*

A study carried out by Jussawalla and others (1970) examined the differences observed in the site incidence of cancer between the Parsi community and the total population of Greater Bombay. This investigation revealed disease differences of appreciable epidemiologic interest. Thus, cancers of the buccal cavity, pharynx, larynx, oesophagus and cervix uteri were less common in the Parsis. On the other hand, the Parsi rates were higher for sites such as the female breast, body of uterus, ovary, prostate and skin and for all leukemias. The purpose of this study is to determine the incidence of various types of cancer by religion. The numerical distribution of religions in Bombay is as follows: Hindus 4,110,746 (68.85%), Muslims 843,358 (14.13%), Christians 375,265 (6.29%), Parsis 64,667 (1.08%), Jains 244,721 (4.10%), Buddhists 284,303 (4.76%), and Sikhs 42,862 (0.71%) out of a total population of 6 million persons. Statistical analysis of the recorded data on cancer will be carried out as follows: (1) Crude and age-specific rates by sex, year and primary sites in various religious groups; (2) age-adjusted rates, as suggested by Doll and others, by sex and primary sites; (3) comparison of incidence rates for religious groups in Greater Bombay with those for other races in the United States and other countries.

81. NASOPHARYNGEAL CARCINOMA AND BURKITT'S LYMPHOMA

Higgenson, J., Centre International de Recherche sur le Cancer, *150 Cours Albert Thomas, 69372 Lyon Cedex 2, France*

OBJECTIVE: Continuation of Burkitt's lymphoma (BL) prospective studies, including epidemiological and virological studies in the West Nile. Malaria-related BL studies where EBV serological tests will be performed on selected portions of the population in Tanzania also will be continued. Analysis of genetic markers associated with NPC will be continued. Two HLAs previously identified in the Chinese from Singapore and Hong Kong NPC will be followed from the Singapore group and search for HLA associated with NPC in Tunisia will also be continued. 'Ia-like' antigens screened previously from serum from multiparous women in the Chinese community in Singapore will be followed. The work on mixed lymphocyte reaction (MLR) and primed lymphocyte transformation for investigation of D locus antigen will also be continued. IARC will maintain the serum bank by aliquoting the serum samples, storing the samples, and maintaining the complete records (clinical and virological testing data).

82. SEARCH FOR APUDOMAS IN HUMAN SALIVARY GLANDS

Benitez Bribiesca, L., Santiago, H., Mendoza, M., Freyre, R., Castillo, G., Hospital de Oncologia, Division de Laboratorios, *AV. Cuauhtemoc 330, Mexico City 7, D.F., Mexico*

OBJECTIVE: To determine the role of cells of the amine precursor uptake and decarboxylation (APUD) system in the neoplastic process in the salivary glands by retrospective analysis of cases at the Department of Pathology, Hospital de Oncologia, Centro Medico Nacional, as of 1965.

METHOD: Blocks of tissue in paraffin will be stained with H plus E, Grimelius, lead hematoxilin, and toluidine blue. Study by electron microscopy of those specimens having blocks in plastic will be performed to identify the presence of neurosecretory granules. Cases of Warthin's tumor will be eliminated. Clinical correlation of cases identified as having tumors composed of APUD cells will be performed. Age, sex, course of disease, infiltration, metastases, serum glucose levels, the presence of diabetes and endocrinopathies will be recorded. Results will be evaluated from a histologic point of view, reclassifying the neoplasias and grouping them as entirely comprised of APUD cells, only partially comprised of APUD cells, or not showing any of these cellular characteristics. The possibility of a clinicopathologic correlation will be determined.

83. FREQUENCY OF CANCER IN SINGLE 'COLD' NODULES OF THE THYROID

Ahumada, J. J., Villabona, G., Mejia, D., Instituto Nacional de Cancerologia, Seccion de Medicina Nuclear, *Apartado Aereo #17.158, Calle 1 No. 9-85, Bogota, DE, Colombia*

OBJECTIVE: To determine the frequency of malignant neoplasia in solitary thyroid nodules showing 'cold' behavior in the gammagraphic study of the gland using radioiodine.

MATERIAL: Clinical histories of the Institute's thyroidectomy patients from January 1973 through December 1977, in whom pre-operative gammagrams made with radioioactive iodine revealed single 'cold' nodules.

METHODS: Analytical study of the above-mentioned clinical histories. (Translated)

84. RELATIONSHIP OF ABO BLOOD GROUPS TO CANCER IN BANGLADESH

Rahim, M. A., Miah, M. N., Sarma, S. K., Sirajoddowla, M., Khaleque, S. A., Kabir, M. A., Dacca Medical College Hospital, Dept. of Radiotherapy & Chemotherapy, *49 E. Azimpur Govt. Estate, Dacca 5, Bangladesh*

The study aims to examine the possible relationship of ABO blood groups to cancer of specific sites - stomach, salivary glands, breast cancer in both sexes, penis, cervix and bone. Normal healthy volunteers will act as controls.

85. FOLLOW-UP STUDY OF LIVER CIRRHOSIS

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More than 10,000 males with liver cirrhosis, divided into categories of age and race, will be followed up over a five to ten year period to determine their overall mortality experience, their site-specific rates of cancer incidence and their cancer risks in relation to levels of tobacco smoked and alcohol consumed. Cirrhotic patients will also be compared with a control group of the same age and race, but without liver cirrhosis, in order to evaluate differences in marital status, religious preference, residence and occupation. Controls and cases will be selected from the 171 United States veterans hospitals located in 48 contiguous states, the District of Columbia and Puerto Rico. This study is a sequel to many previous studies on United States veterans which, generally, found increased risks of floor of mouth, uvula and soft palate, pharynx, esophagus and liver cancers among cirrhotics, heavy smokers, heavy drinkers or among patients with combinations of these attributes.

86. OTOPATHOLOGY BY LIGHT MICROSCOPY

Schuknecht, H. F., Goodloe Greene, L. J., Kitamura, K., Walby, P., Massachusetts Eye & Ear Infirmary, Dept. of Otolaryngology, *243 Charles St., Boston, Massachusetts*, 02114, United States of America

Human temporal bones will be collected at autopsy from subjects who had hearing loss, vertigo, facial palsy or neoplasia of the ear. The specimens will be prepared for histological study and the pathological findings will be quantified for comparison with the clinical manifestations. Ganglion cell counts will be done of both the auditory and vestibular nerves and hair cell losses will be recorded for the organ of Corti, cristae, and maculae. Attempts will be made to provide new information on the etiology, pathophysiology and therapy of otologic disease.

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G. OTHER EPIDEMIOLOGICAL STUDIES OF ORAL AND HEAD AND NECK CANCER

87. HIDRADENOMATA OF THE EXTERNAL EAR CANAL (CERUMINOMAS)

Pahor, A. L., Jones, E. L., Dudley Road Hospital, Dept. of Otorhinolaryngology & Head & Neck Oncology, *Dudley Rd., Birmingham B18 7QH, England, United Kingdom*

Hidradenomata of the external auditory meatus are uncommon tumors. All reports so far are either single or concern a few cases from a selected group of patients, usually hospital-based, and show confusion regarding the pathology and nature of these tumors. The present study aims to analyze the cases diagnosed and managed in the West Midlands over a number of years, using data collected from the Birmingham Regional Cancer Registry which are likely to be more representative of the true incidence and survival than series from individual hospitals. A previous report appeared in J. Laryng. 89:707-720, 1975.

88. EXTRAMEDULLARY PLASMACYTOMA (EMP) OF THE HEAD AND NECK

Pahor, A., Waterhouse, J. A., Powell, J., Dudley Road Hospital, Dept. of Otorhinolaryngology & Head & Neck Oncology, *Dudley Rd., Birmingham B18 7QH, England, United Kingdom*

Extramedullary plasmacytomas are rare tumors and present difficulty in diagnosis for both the clinician and the pathologist. A study of a group of these tumors is of value to throw some light on their nature, presentation and natural history until diagnosis (which can be years). This present study aims to update a previous study (J. Laryng., 91, 241-258, 1977) and follows a previous report (J. Laryng., 92, 223-232, 1978). Data collected from the Birmingham Regional Cancer Registry is analyzed and emphasis will be laid on incidence in the general population, sites affected, age, sex, and survival, comparing these with similar data for multiple myeloma.

89. CANCER OF THE UPPER LIP

Lindqvist, C. J., Teppo, L., Finnish Cancer Registry, *Liisankatu 21 B, 00170 Helsinki 17, Finland*

The epidemiology of lip cancer has been thoroughly studied during recent years in Finland (Am. J. Epidemiol., 109, 521-530, 1979). Cancer of the upper lip has, however, not been analyzed separately. Differences in male/female ratios of the incidence rates, time-trends, age-incidence curves, urban/rural ratios and geographical distribution in the different provinces of Finland suggest that the risk factors in upper and lower lip cancers may be different. The material consists of all cases of cancer of the upper lip diagnosed in the years 1953-1975 and reported to the Finnish Cancer Registry. The epidemiology of upper lip cancer will be studied, and compared and correlated with data on total lip cancer together with some other types of cancer with the aim of testing certain etiological hypotheses.

90. HOSPITAL BASED CANCER REGISTRY IN VISAKHAPATNAM

Chintala, R., Andhra Medical College, Dept. of Pathology, *Visakhapatnam 530002, India*

Palatal cancer is very common in this area in both sexes. Among males, penile cancer is also very common. A hospital-based cancer registry was established in 1976 to evaluate the frequency of these cancers. All cancer cases (histologically confirmed in the Department of Pathology) coming from a defined geographical area with a population of one million are collected. The minimum rates per thousand are calculated and standardized by age according to WHO.

91. BANGLADESH CANCER EPIDEMIOLOGY RESEARCH PROGRAM (BCERP)

Rahim, M. A., Ahmed, Q. A., Kabir, M. A., Elahi, M. F., Hossain, M. A., Islam, K. M., Khair, M. A., Khaleque, S. A., Miah, M. N., Pati, B. P., Sarma, S. K., Haque, N., Dacca Medical College Hospital, Dept. of Radiotherapy & Chemotherapy, *49 E. Azimpur Govt. Estate, Dacca 5, Bangladesh*

The aim is to examine the relative frequency of all cancers. Hospitals where radiotherapy facilities are available have been selected for the study. Participation of other hospitals which lack a radiotherapy center is voluntary. Consultants attached to participating hospitals are co-investigators. After interview and examination a clinical report is prepared, one for each patient, in the ad hoc tumor registry of BCERP. The records are collected centrally for compilation and statistical analysis. Three articles have been published and results show that cancer of the lerynx, lung and oropharynx is frequent in males, and cancer of the cervix, breast and oral cavity is frequent in females.

92. EPIDEMIOLOGICAL ASPECTS OF A CANCER CONTROL PILOT PROJECT

Narayanan, M., Arignar Anna Memorial Cancer Inst., Dept. of Gynaecology, *Railway Rd., Kanchipuram 631501, Tamil Nadu, India*

Within the framework of a program for the early detection of precancerous lesions and early cancer of the uterine cervix, oral cavity, and pharynx, by systematic clinical examination, cytology and biopsy, aetiological and epidemiological studies will be undertaken. The prevalence and incidence of these cancers will also be assessed. Knowledge, attitudes and practices relating to cancer are being examined in relation to a large number of factors including age, sex, religion, occupation, income, etc. Questions are asked about diet, personal habits, reproduction associated factors, etc.

93. EPIDEMIOLOGY AND PATHOLOGY OF CANCER IN MALAWI

Hutt, M. S., Burkitt, D. P., Borgstein, J. L., Tozer, R. S., Molyneux, M., Cook, P., Lucas, S., University of London, St. Thomas' Hospital Medical School, Dept. of Morbid Anatomy, *Lambeth Palace Rd., London SE1 7EH, England, United Kingdom*

All pathological specimens from Malawi for the last 10 years have been examined in St. Thomas' Hospital Unit of Geographical Pathology. Analyses of the epidemiological features of Kaposi's sarcoma and of precancerous and cancerous lesions of the conjunctiva have been completed; studies of salivary gland neoplasms, malignant histiocytosis and solitary myeloma are under way.

94. EPIDEMIOLOGY OF ORAL SQUAMOUS CELL CARCINOMA

Johnson, N. W., Langdon, J. D., Evans, S., Hopps, R. M., Rapidis, A., University of London, London Hospital Medical College, Dept. of Oral Pathology, *Turner St., London E1 2AD, England, United Kingdom*

Over 300 cases of oral squamous cell carcinoma treated at the London Hospital Medical College are being analyzed in a case characteristics study which aims to determine high risk groups and to establish what factors affect prognosis (e.g., site, age, sex, etiology, size of lesion at presentation, rate of tumor growth and histopathological category). The study is both retrospective and prospective. A modification of the TNM grading and staging system is being evaluated. Data are analyzed using the statistical package for the social sciences with corrections for age employing both the Peto and Peto method and the Cox method.

95. CANCER IN THE IGBOS OF NIGERIA

Onuigbo, W. I., Medical Foundation, *8 Nsukka Ln., Uwani, P.M.B. 1098, Enugu, Nigeria*

This ongoing study of the relative frequency and the characteristics of cancer cases biopsied in different hospitals serving the Igbos of Nigeria and examined personally has resulted in the publication of data on tumors of the skin, eye, vulva, cervix, ovary, testis, alimentary tract, liver, oral cavity, lip and jaw. The most recent publications on tumors are: Schistosomiasis of ovarian thecoma (Med. J. Zambia, 12, 27-28, 1978) and adolescent breast masses in Nigerian Igbos (Amer. J. Surg., 137, 367-368, 1979). Work continues.

96. CANCER REGISTRY COVERING MEMBERS OF SOCIAL SECURITY SYSTEM

Espinosa de Restrepo, H., Franco Henao, A., Agudelo, U., Inst. de Seguridad Social, *Apartado Aereo 59-09, Medellin, Colombia*

A cancer registry was initiated in the Social Security Institute in Medellin in 1972. Efforts were made to register all cases of cancer diagnosed for the first time since 1st January 1968. The objectives of this cancer registry covering a selected population are: (1) to obtain data on incidence and mortality from cancer; and (2) to undertake analytical studies to determine the relation of risk factors to specific types of cancer in groups with defined occupations and other socioeconomic characteristics. The first five years of registration showed differences for skin, larynx, and oral cancer compared to the general population. Another interesting finding was the high incidence of stomach cancer in males native to certain parts of the region (Antioquia). These findings are subjects of special studies at the present.

97. HEAD, NECK AND LARYNX CANCERS

Dijkstra, B. K., Haynes, D., Kay, S., Brown, H., University of the Witwatersrand, Head, Neck & Larynx Cancer Clinics, Dept. of Ear, Nose & Throat, *c/o General Hospital, Johannesburg, South Africa*

A questionnaire is being designed to collect data from all cases of larynx, head and neck cancer to be stored on computer to provide a basis for future research. Data on an estimated 2,500 patients from the General Hospital are on record from 1970 and will also be put on computer.

98. EPIDEMIOLOGY OF NEOPLAMS OF SALIVARY GLANDS IN ROCHESTER

Bouquot, J. E., Mayo Foundation, Dept. of Medical Statistics & Epidemiology, *200 1st St. S.W., Rochester, Minnesota,* 55901, United States of America

This is part of a broader project. A summary of this subproject is not available.

99. INCIDENCE OF CARCINOMA OF THE ORAL CAVITY, PHARYNX, LARYNX, NASAL SINUS AND PARANASAL SINUSES IN ROCHESTER, MINNESOTA, 1935-1974

Bouquot, J. E., Lovested, S. A., Weiland, L. H., Elveback, L. R., Kurland, L. T., West Virginia University, School of Medicine, Dept. of Oral Pathology, *Medical Ctr. Dr., Morgantown, West Virginia,* 26506, United States of America

This is a descriptive study of the incidence of cancer of the oral cavity, pharynx, larynx, nasal and paranasal sinuses in Rochester during a 40-year period.

100. ORAL, PHARYNGEAL, LARYNGEAL AND NASAL MALIGNANCY IN OLMSTED COUNTY, 1935-74

Bouquot, J. E., Mayo Foundation, Dept. of Medical Statistics & Epidemiology, *200 1st St. S.W., Rochester, Minnesota,* 55901, United States of America

This is part of a broader project. A summary of this subproject is not available.

II. EXPERIMENTAL CARCINOGENESIS AND PATHOLOGY

A. EXPERIMENTAL CARCINOGENESIS AND RELATED BIOLOGY

101. FIBROUS CARCINOGENS IN TURKESTAN FLOUR

O'Neill, C. H., Jordan, P. W., Hodges, G. M., Newman, R. H., Imperial Cancer Research Fund, Anchorage Dependence Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Esophageal cancer is a major cause of death in parts of Turkestan. The local distribution of the disease in this region, and its occurrence in certain other remote arid parts of the world, point to an environmental cause.

We have now been able to identify a sharply pointed silica fiber, about two hundred microns in length and three in diameter, as a common contaminant of the flour from this region. It is not present in European flour, or in flour from various villages in Turkey and Syria. It originates from the surface of the seed of a species of grass, Phalaris genus, which can readily be identified in the wheat because of its characteristic morphology. X-ray scattering distinguishes it from fibers of mineral origin such as asbestos and shows it to be pure silica. While we do not know how fibrous carcinogens act, we have in the past shown that they can stimulate the growth of cultured fibroblasts. Tissue culture experiments have now shown that Phalaris fibrils similarly cause conspicuous and immediate stimulation of the proliferation of 3T3 cells in soft gel suspensions, ultimately resulting in the production of large colonies.

During the course of the last year investigations in Iran have shown that 80 percent of the people in the affected areas suffer from esophageal dysplasia (leucoplakia). We have therefore instituted animal experiments to determine whether Phalaris fibers can cause similar dysplasia in mice, and whether they can promote the appearance of tumors initiated by chemicals. It is hoped that this work may eventually stimulate epidemiological testing of this hypothesis either in Iran or in the other affected regions (the Transkei and the area around Lin-Hsien in China).

102. ENHANCED ORAL CARCINOGENESIS BY LOW DOSE X-RADIATION

Lurie, A. G., University of Connecticut, Health Center, School of Dental Medicine, Dept. of Oral Diagnosis, *Farmington Ave., Farmington, Connecticut,* 06032, United States of America

The tissues of the human oral cavity are frequently exposed to repeated low doses of known and suspected carcinogens such as tobacco and x-radiation from diagnostic medical and dental sources. Prior studies in our laboratory have shown synergy between concurrent applications of DMBA and exposures to modest levels of x-radiation in hamster cheek pouch tumorigenesis. This synergy was manifested by greater tumor incidence, shorter latent period, and greater tumor volume in animals receiving combined treatments than in animals receiving either treatment alone. We have also shown that low-level x-radiation causes a significant late increase in pouch vascular volume and that there is a significant interaction between the effects of x-radiation and DMBA-induced tumors on pouch functional vasculature. Ongoing studies are examining the effects of decreasing radiation doses on DMBA-induced tumor incidence and progression as well as the possible mechanistic role of radiation-induced hemodynamic changes in the induction and progression of these tumors. Young adult male Syrian golden hamsters have received various doses of DMBA to the cheek pouch accompanied by repeated exposures of 1-20R x-radiation at weekly intervals. The temporal relationships between applications of the chemical and radiation have varied. Animals are being observed for varying lengths of time; tumor latency, volume, incidence, histopathology and hemodynamics are being studied using observational, histopathological and radioisotopic techniques. It is anticipated that the results of these studies will clarify dose-response relationships and time-dose relationships of low level x-radiation in this system, leading to a more quantitative basis for calculations of human radiation risk estimates. Additionally, the data should provide information on the nature of radiation induced hemodynamic changes in the induction of epithelial neoplasms by low level exposures to multiple environmental carcinogens.

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103. STUDIES ON CANINE ORAL PAPILLOMATOSIS

Tokita, H., Chiba Cancer Center Research Inst., Division of Animal Research, *666-2, Nitona-Cho, Chiba 280, Chiba, Japan*

OBJECTIVE: Canine oral papilloma virus has been known to possess strict host and tissue specificity. The present study was undertaken to ascertain the oncogenic potential of COPV in a variety of tissues and organs of dogs.

APPROACH: The virus was inoculated into some organs of dogs. Canine oral papilloma cells were cultivated in vitro.

PROGRESS: Papillomatous tumors were induced in the oral mucosa, cornea, conjunctiva, eyelid, and the skin. Humoral antibodies against tumor extracts were detected by complement fixation test and immune adherence test. Antigens and antibodies related to papilloma cell surface were detected by immune adherence test and cytotoxicity test.

104. TRANSFORMATION OF ORAL MUCOSA BY HERPES SIMPLEX VIRUS

Schuster, G. S., Erbland, J. F., Singh, B. B., Medical College of Georgia, School of Dentistry, Dept. of Oral Biology, *1459 Gwinnett St., Augusta, Georgia,* 30902, United States of America

The current research is intended to examine the ability of herpes simplex viruses, alone and in combination with chemical carcinogens, to function in transformation of the oral mucosa. The studies concentrate on changes in the cell surface structures and components, particularly alterations in lipids, glycolipids and glycoproteins, that occur in the early time periods following infection. These components are known to affect cell social behavior and tissue differentiation, and change following viral and chemical induced transformation. Mucosal tissues are grown in vitro and infected with herpes simplex viruses which have been shown to have the ability to transform cells. At varying periods of time following infection, the explanted tissues are harvested and examined for chemical changes in the cell lipid, glycolipid and glycoprotein componets. Neutral lipids and phospholipids are separated and identified by column, paper and gas chromatography and autoradiography. Glycolipids are to be separated by thin layer chromatography and autoradiography. Glycoprotein determinations are made by radioactively labeling glycoproteins which will subsequently be separated by acrylamide gel electrophoresis and radioactivity will be determined. Enhancement of transformation by chemical will be determined using cultures of epithelial cells infected with virus or treated with virus and a chemical carcinogen. The relative ability of the chemical to increase virus induced transformation will be determined. In addition, it is proposed to attempt to develop a method of culturing epithelial cells using conditioned medium or cell extracts, rather than the feeder layers of irradiated 3T3 fibroblasts. Morphological studies on epithelial tissues will be conducted at an ultrastructural level to supplement the analytic studies and demonstrate decreased numbers and altered shapes of microvilli and fewer as well as fewer and smaller intercellular junctions.

105. CHEMICAL CARCINOGENESIS IN CYST INDUCED IN PRIMATES

Jonck, L. M., Raubenheimer, E. J., University of Pretoria, School of Dentistry, Institute of Stomatology, *P.O. Box 1266, Pretoria 0001, Transvaal, South Africa*

The carcinogenic action of nitrosamine derivates is well known. The aim of this project is to induce neoplastic change in an experimental cyst model developed after implantation of oral epithelium in the back muscles of immunosuppressed monkeys.

In this experiment particular attention will be paid to the concentration of the carcinogen and the time lapse to affect neoplastic change in oral epithelium. An attempt will also be made to study the influence of drugs used in dentistry known to be correlated with nitrosamines.

106. STUDIES ON VITAMIN A TREATED HAMSTER CHEEK POUCH EPITHELIUM ON EXPOSURE TO LIME AND TOBACCO - OPTICAL HISTOPATHOLOGY AND ULTRASTRUCTURE

Kandarkar, S. V., Sirsat, S. M., Cancer Research Inst., Dept. of Ultrastructure, *Dr. Ernest Borges Marg, c/o Tata Memorial Ctr., Bombay 400012, Maharashtra, India*

OBJECTIVE: The high incidence of oral cancer in India has been attributed to the chewing of tobacco either singly or as a part of the betel quid. However, attempts at the induction of malignancy in laboratory animals by exposure to ingredients of betel quid were unsuccessful. This investigation was another attempt to induce tumor with ingredients of the betel quid - lime and tobacco singly and in combination - in the hamster cheek pouch parallely conditioned by exposure to vitamin A which is known to enhance DMBA carcinogenesis in the identical animal system.

EXPERIMENTAL APPROACH: Fifty inbred Syrian hamsters kept on a standard laboratory diet were divided into two groups. In the first group, the cheek pouches of animals were painted thrice a week with both lime and tobacco. In the second group the animals were treated with lime and vitamin A dissolved to a strength of 15 percent in olive oil and then a quid of finely powdered tobacco was inserted in the cheek pouch. All animals were kept until their natural death. This experiment is in progress. Abnormal changes found in this experiment after 52 weeks were keratinization anomalies, dysplastic epithelium with acanthosis, edema and inflammation. Submicroscopically the changes were as follows: damaged and broken basement membrane, increased keratohyalin and membrane coating granules, large unoriented tonofibrils, loss of cytoplasmic organelles and a large number of intercellular spaces. These changes are enhanced in the hamster cheek pouch parallely conditioned by exposure to vitamin A palmitate. The presence of these changes further initiated a study on the effect of lime and tobacco on vitamin A pretreated hamster cheek pouch for the entire life span of the animals instead of controlled periods of exposure to see whether the marked dysplasia led to frank malignancy.

107. ORAL FLORA AND CARCINOGENESIS OF DENTAL THERAPEUTICS

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The objective of this research is to establish the role of the oral flora in affecting the host's response to possible carcinogens in the environment. Concern about exposure to possible mutagenic and carcinogenic agents has stimulated the development of test systems to warn of the presence of such compounds. Metabolic reactions of potential significance to carcinogenesis (azo, nitro, reduction; nitroso formation and degradation) will be examined to ascertain whether the oral flora is capable of playing a role similar to that of the intestinal flora as being important in the activation or deactivation of potential carcinogens. Initially dental therapeutics and tumorigenic agents in cigarettes will be tested because of their chronic exposure and application to the oral mucosa. DNA damage that may result from exposure to various dental therapeutic agents (chemicals) will be quantitated using the Ames in vitro mutagen test system. This method maximizes detection of DNA damage by Salmonella typhimurium mutants in vitro. The usefulness and sensitivity of the above in vitro method has been improved by infecting germ-free rats with the Salmonella mutant. This model incorporates bacterial metabolism and mammalian physiology by maintaining the bacterial mutants in the oral cavity and gastrointestinal tract. This is advantageous since these bacteria would then function as a biological probe, indicating the DNA damaging ability of chemicals under conditions present in the actual animal. An important advantage of this model is that the bacteria normally present in the oral cavity and gastrointestinal tract can be added into the rat in selected ways so their role in carcinogenesis (vis-a-vis mutagenesis) can be evaluated under well-controlled conditions. Using these techniques we hope to identify potential carcinogens (therapeutic agents) as mutagens and determine the role of the oral and intestinal flora in the carcinogenic process.

108. STUDIES OF NASAL CANCER IN WORKERS EXPOSED TO NICKEL AND DEVELOPMENT OF METHODS FOR SCREENING AND EARLY DIAGNOSIS (ABBREV)

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OBJECTIVE: Histopathological follow-up study of known cases and screening for new cases of precancerous lesions by light microscopy (LM). Characterization of normal, metaplastic, dysplastic (precancerous) and cancerous lesions of the nasal mucosa by means of scanning and transmission electron microscopy (SEM, TEM), morphometry, autoradiography (cell kinetics), and development of cytological screening methods for cancerous and precancerous lesions and an experimental model using rats for upper airway carcinogenesis.

APPROACH: Biopsies from the nasal mucosa of workers in a nickel refinery were plastic-embedded for histopathology and morphometry. A method was introduced for characterization of large mucosal areas by SEM and, thereafter, areas of interest were sectioned for comparison with LM and TEM. Cytological samples from the regions adjacent to the biopsy were taken with a special brush. A new model was developed for morphometric characterization of the different histopathological stages of nasal mucosa.

We will now develop an experimental model with rats for inhalation and installation of carcinogens to be used for comparison with the pathological alterations seen in human nasal mucosa. Furthermore, cytokinetic evaluation will be made by in vitro incubation in tritiated thymidine.

PROGRESS: The histopathological follow-up study has shown a marked decrease in the number of cases with dysplasia, probably as a consequence of the environmental conditions in the refinery in recent years. Our morphometric studies show that different histopathological stages can be characterized objectively (Pathology: Research and Practice, in press). The SEM studies have shown that the different stages are also reflected in different surface structures of cells at the luminal site.

109. PRETREATMENT OF NUDE MICE FOR INCREASING HETEROTRANSPLANTABILITY OF HUMAN CANCER TISSUES

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OBJECTIVE: Although a number of human cancers have been successfully transplanted in athymic nude mice, the rate of successful heterografts is generally low and limited to certain types of cancer. We have undertaken a series of experiments for improving the rate of tumor takes.

APPROACH: A cultured cell line derived from human nasopharyngeal carcinoma, NPC204, has a critical threshold of cell inoculum for tumor take when transplanted in untreated nude mice. We transplanted the cells at different cell doses to nude mice under one or combination of the following conditions that influence host resistance to heterotransplantation: (a) age of animals, (b) dose of whole body irradiation, and (c) splenectomy.

PROGRESS: (1) The non-lethal dose of 400 rads did not affect animal growth and suppressed host resistance to heterotransplantation in adult mice. (2) Tumor takes were more frequent in 5-day-old mice than in 4-week-old ones. (3) Splenectomy in young animals did not increase significantly the rate of tumor take. (4) The combination of adult splenectomy and irradiation at 400 rads increased frequency of tumor take. (To be published in Jpn. J. Exp. Med.)

110. ENHANCEMENT OF ORAL CANCER AFTER ALLOGRAFTING

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The proposed investigation concerns itself with the observation that organ allograft recipients have a greater risk of developing squamous cell carcinoma of the labial mucosa as well as other types of cancer.

I hypothecate that the increased incidence of cancer is, at least in part, a result of the generation of suppressor cells induced by the allograft antigens and that these cells nonspecifically reduce the immune response to nascent tumors arising in the allograft recipients. This hypothesis is supported by preliminary experimental evidence presented by myself and others.

The need for this hypothesis has been necessitated by the numerous investigations which have shed doubt on the efficacy of the classical immunological surveillance system as an explanation for the observed increased incidence of neoplasia in allograft recipients. In order to support my hypothesis, four major questions are asked in this proposal: 1. Do allografted mice have an enhancement of syngeneic tumor growth? 2. Is the antitumor immune response reduced in the allografted recipients? 3.

Is the reduction of the anti-tumor immune response due to suppressor cells within the spleens of the allografted mice? 4. Are the suppressor cells T cells or macrophages?

111. ETHANOL AND THE ETIOLOGY OF ORAL CANCER (HAMSTERS)

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This is part of a broader project. A summary of this subproject is not available.

112. ANALYSIS OF SALIVARY GLAND TRANSFORMATION IN VITRO USING CELL HYBRIDIZATION TECHNIQUES

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A number of studies on hybrids constructed between normal and malignant cells have shown that the presence of chromosomes from the normal parent can suppress expression of the malignant phenotype in the hybrid. We are in the process of constructing intraspecific hybrids between salivary epithelial cells at various stages in the transformation process - normal cells, cells from preneoplastic foci in primary culture and cells from preneoplastic and carcinoma-producing cell lines. We plan to analyse the ability of a range of hybrids to produce tumors in vivo and correlate this with other parameters such as expression of in vitro markers of transformation, growth in agar in particular, and chromosome complement. It will not be possible to determine from which parent individual normal chromosomes were derived but the role of marker chromosomes characterizing some of the cell lines can be assessed.

Since none of our epithelial cell lines carry selectable genetic markers, we have used a method whereby parental cells are treated with a lethal dose of different biochemical inhibitors immediately before fusion with polyethylene glycol (Wright, Experimental Cell Research 1978, 112, 395). We treated cells in suspension with iodoacetamide (3-5mM) or diethylpyrocarbonate (0.005-0.0075 percent) for 30 minutes on ice. This was followed by fusion, using 40 percent PEG 1000 added to the pellet of pooled cells that had been pretreated with 100 micrograms/ml phytohemagglutinin. This enhances fusion efficiency and reduces the toxicity found at higher concentrations of PEG (Mercer and Schlegel, Experimental Cell Research 1979, 120, 417). Provided that toxicity in unfused parental cells or in homotypic fusions is monitored in each experiment, the probability that dividing colonies are derived from heterotypic fusions is near 100 percent. Identification of marker chromosomes in presumptive hybrid clones can confirm their origin.

113. THE EFFECT OF CYTOCHALASIN B-INDUCED TETRAPLOIDY ON SALIVARY GLAND TRANSFORMATION

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We are studying the role of tetraploid formation in the generation of malignant salivary epithelial cell lines in an in vitro chemical carcinogenesis system. All tumorigenic cell lines are subtetraploid and probably derive from the tetraploid population of cells that arises during Stage III of the system and forms 20-60 percent of the population in each focus of abnormal, slowly dividing, preneoplastic cells (ICRF Scientific Report 1978 - report 152). Optimum conditions have been established for treating normal salivary gland epithelial cells with cytochalasin B (CB) in order to induce tetraploid formation in cells in early explant outgrowths. Primary explant cultures are exposed continuously to 1.0 microgram/ml CB over a three-day period of active cell proliferation (day 3-6). Under these conditions, 30 percent of the quiescent outgrowth has a 4C DNA content, measured in situ at four weeks. In control solvent-treated cultures, only 5 percent of the outgrowth cells have 4C DNA content values. If CB treatment is continued for four days, 50 percent of the outgrowth cells at four weeks have a 4C DNA content but the total numbers of cells are considerably reduced. We are now determining the effect of experimental induction of tetraploidy in carcinogen-treated or untreated epithelial cells, in particular on the timing and frequency of appearance of Stage III preneoplastic foci and on their progression to malignant Stage IV cell lines. We are investigating the use of agents other than CB which induce tetraploidy by different mechanisms.

114. CLONAL ANALYSIS OF BIOLOGICAL HETEROGENEITY IN PRENEOPLASTIC SALIVARY GLAND CELL LINES

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We have previously described (ICRF Scientific Report 1978 - report 137) several preneoplastic epithelial cell lines derived from foci of abnormal Stage III cells tranformed by chemical carcinogens in vitro. Stage III foci in primary culture are heterogeneous in their capacity for growth in serially passaged culture and in their potential for transition to Stage IV, characterized by the ability to produce tumors in syngeneic mice. We are attempting to obtain evidence for the preliminary indication that heterogeneity is influenced by conditions early in the culture history, such as carcinogen treatment protocol.

We are also studying the heterogeneity within and between different lines of preneoplastic epitheial cells during their progression to Stage IV. We have isolated a number of sister clones from early passages of each cell line, in order to compare characteristics and assess the role of clonal selection in the acquisition of tumorigenicity. The two best studied lines, CSG 205 clone 2B1 and CSG 211, differ in two respects, their capacity for growth in soft agar and their response to the tumor promoter, TPA. CSG 205/2B1 produces carcinomas at about passage (P) 20, but at P33 still shows no growth in soft agar into which 10 to the power 6 cells have been seeded per 5cm dish with feeder cells. In contrast, CSG 211 acquires the capacity to grow in soft agar (colony forming efficiency equals 0.07 percent) under the same conditions, at about the passage level that first produces carcinomas (P27).

Weekly treatment with TPA stimulates growth of preneoplastic CSG 205/2B1 compared to parallel solvent-treated cultures but does not affect the timing of Stage IV change. In contrast, TPA inhibits growth in CSG 211 but preliminary evidence suggests that it may accelerate the onset of Stage IV in this cell line relative to parallel sovent-treated cultures. Biological behavior can be related to chromosome complement in the parental lines (see Report 132) and to sister clones derived from them. The aim is to identify specific, possibly necessary changes involved in the evolution of malignancy and associated in vitro markers of transformation.

115. CHROMOSOME CHANGES ASSOCIATED WITH TRANSFORMATION OF MOUSE SALIVARY GLAND EPITHELIUM

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Changes in DNA content during in vitro transformation of mouse salivary gland epithelium has been described previously (ICRF Scientific Report 1978 - report 152). All tumorigenic cell lines transformed in vitro, or from tumours induced in vivo, had DNA contents in the subtetraploid range. This has been confirmed using conventional metaphase chromosome preparations and all but one line (from a carcinoma induced in vivo) have modal chromosome numbers in the 63-73 range (2n equals 40). The exception has a bimodal distribution with a sub-octaploid component. A full analysis of the chromosome complement in each cell line, using the trypsin-giemsa banding technique, is nearly complete. It is hoped that consistencies may exist between different lines and that comparisons can be made with information from a similar study of transformed mouse bladder epithelial cell lines (Report 141). It will be of particular interest to follow the development of chromosome patterns typical of these cell lines where stocks are available of the early passage, preneoplastic cells.

116. MICROCOCCAL NUCLEASE STUDIES OF CHROMATIN IN MOUSE SUBMANDIBULAR SALIVARY GLAND

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Micrococcal nuclease digestion studies have provided important information with respect to chromatin structure in eukaryotic cells (Thomas, International Review of Biochemistry 1978, 17, 181). Furthermore a method has recently been reported for the purification of eukaryotic cell euchromatin using low-level micrococcal nuclease treatment of purified nuclei (Tata and Baker, Journal of Molecular Biology 1978, 118, 249).

Mouse salivary gland nuclei were stabilized during cellular homogenization by the addition of polyamines and Ca2 ion to high molarity sucrose (o.88M sucrose/buffer A/1.8mM CaCl2, pH7.4) containing the protease inhibitor Aprotinin. (Buffer A equals 60 mM KCl, 15 mM NaCl, 0,15 mM spermine tetrahydrochloride, 0.5 mM spermidine trihydrochloride, 15 mM betamercaptoethanol, 15 mM Tris-HCl, pH 7.4.) Centrifugation of the nuclei through 2.2M sucrose/buffer A resulted in a yield of 20 percent of DNA in nuclei that are free of cytoplasmic marker enzyme contamination.

The digestion kinetics with micrococcal nuclease were similar for mouse salivary gland and liver chromatin. Solubilization reaches a plateau at 50-60 percent of chromatin in the region of 50-250 enzyme unit minutes. Digestion beyond this level resulted in chromatin aggregation and precipitation from solution.

The initial solubilization product of chromatin from salivary gland and liver at 37 degrees C was a quasi-stable high molecular weight species of some 15-20 nucleosomes length. This species may reflect higher order chromatin organization under these preparation conditions. Subsequently the chromatin was converted to smaller subunits including mononucleosomes of 140-200 base pair size and subnucleosome species. The mononucleosome from salivary gland had S20.w equals 11s and contained the core histones H2A, H28 H3 and H2. This study of salivary gland chromatin is currently being used as a basis for a comparison of total chromatin-associated proteins in normal and chemically transformed epithelial cells and for the purification of the euchromatin fraction from such cells.

117. EUCHROMATIN PROTEINS IN NORMAL AND CHEMICALLY TRANSFORMED EPITHELIAL CELLS

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The transcriptionally active euchromatin fraction of chromatin may undergo important changes with alteration of a cell to the transformed state. Recently, techniques have been reported for the purification of the RNA polymerase II-associated euchromatin fraction by low level micrococcal nuclease digestion of whole nuclei (Tata and Baker, Journal of Molecular Biology 1978, 118, 249).

Micrococcal nuclease studies on submandibular salivary gland chromatin (see Report 151) are being extended in order to prepare the euchromatin fraction from control and chemically transformed tissue explants and cell lines. These cells will be compared with respect to the profile of euchromatin proteins in an attempt to detect alterations which are related to cellular transformation.

Preliminary results with salivary gland explant cells indicate that more extensive digestion with micrococcal nuclease is required than has previously been reported for preparation of the euchromatin fraction. This result appears to be due to increased chromatin condensation with polyamine stabilization of nuclei (see Report 151). Low level digestion results in solubilization of polynucleosomal species of chromatin which are currently being examined for association with RNA polymerase II. The protein profiles of the enzyme-associated species will be examined by sodium dodecylsulphate gel electrophoresis and O'Farrell 2-dimensional NEPHGE electrophoresis (O'Farrell, Cell 1977, 12, 1133).

Changes in the euchromatin proteins that occur with cell transformation may provide valuable information with respect to the alterations in gene activity that occur with transformation. Furthermore, such proteins will be useful markers for the detection of transformed cells.

118. ULTRASTRUCTURAL STUDIES ON MICROCOCCAL NUCLEASE-DIGESTED EPITHELIAL CELL CHROMATIN

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Electron microscopy has yielded valuable information with respect to chromatin structure and its relationship to different states of cellular activity (Oudet et al., Cold Spring Harbor Symposia on Quantitative Biology 1977, XLII, 301). Furthermore, nuclease digestion studies have proved useful in determining the structural relationships between proteins and DNA in chromatin (Van Holde and Weischet in 'The Cell Nucleus' Busch, ed. 1978 4, 75).

The gross- and fine-structure of chromatin is being compared in normal and transformed epithelial cells in order to examine the effects of micrococcal nuclease on chromatin structure during selective solubilization of euchromatin.

Normal salivary gland chromatin shows a high degree of chromatin condensation in the presence of the nuclear stabilizing polyamines spermine and spermidine. Microccocal nuclease digestion under these conditions results in the selective digestion of the euchromatin-like filaments. A direct assessment of the euchromatin under these conditions is being performed using the Miller spreading technique in an attempt to visualize directly the transcriptional complex and to assess the response of this complex to micrococcal nuclease treatment. The analysis is presently being extended to a range of transformed salivary gland epithelial cell lines.

This study provides a direct approach to the question of differences in chromatin organization in normal and transformed cells.

119. PROTEINS IN NORMAL AND CHEMICALLY TRANSFORMED EPITHELIAL CELLS

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Immunological procedures have provided useful information with respect to chromatin organization (Goldblatt et al., Experimental Cell Research 1978, 112, 1) and alterations in chromatin with cellular transformation (Chin et al., Cancer Research 1975, 35, 913).

An antiserum has been raised against the chromatin subunit, the mononucleosome, purified from mouse submandibular salivary gland cells. The antiserum reacts with several proteins, presumably histones, internal to the mononucleosome, as well as DNA-serum albumin complexes. The antiserum is sensitive to alterations in chromatin conformation which are caused by digestion of chromatin with exogenous micrococcal nuclease. These results suggest that the antiserum will be a useful probe of euchromatic and heterochromatic chromatin.

Following its complete characterization the antiserum will be used to compare chromatin in normal and chemically transformed cells with respect to: 1. the conformational state of chromatin measured by the level of cross-relativity with the antiserum; and 2. the number of cross-reacting protein species present in cell chromatin.

This study represents a first approach to the investigation of the amount of euchromatin and the fundamental structural organization of chromatin in normal and chemically transformed cells.

120. STEM CELLS IN ORAL MUCOSA

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The normal structure of the oral mucosa is maintained by continuous cell proliferation of the epithelium. For some other tissues, there is evidence that only a small fraction of the proliferative cells, stem cells, have the ability to divide indefinitely. These cells are responsible for providing the differentiating cells during normal turnover and for regeneration of the tissue following wounding and radiation damage. They may have unusual patterns of differential division. Although it is probable that stem cells exist in oral mucosa, and have important implications for oral disease, they have not yet been clearly identified.

Pilot experiments have indicated the presence of a small number of mucosal epithelial cells which have an atypically long cell cycle and may be stem cells. The proposed research will employ techniques of light and electron microscopic autoradiography, histochemistry and cell culture in further studies of these cells in order a) to examine their function as stem cells, b) to determine their number and distribution in relation to tissue architecture, c) to investigatate their rate of normal proliferation and patterns of division, and d) to investigate their 'clonogenic' abilities. As it is postulated that stem cells play an important role in carcinogenesis, the response of these cells during induction of hyperplasia will be investigated.

121. SEQUENTIAL ANALYSIS OF ORAL CARCINOGENESIS

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The overall objective of the proposed research is to identify and analyze, in sequential fashion, the key pathological changes which occur during oral carcinogenesis. Carcinogen-altered basal cells, chemically induced in hamster buccal pouch epithelium, will be visualized using histological whole-mount preparations suitable for microscopic inspection of the entire basal epithelial layer. The functional property of 'resistance to cytotoxicity,' (the ability to proliferate in a cytotoxic environment inhibitory for normal cells), established architectural criteria, and 'carcinogen-dose-dependency,' will serve as tentative markers for the early detection and quantitation of altered basal cells which are likely initiation sites from which oral cancer can evolve. Once developed, the rapid quantitative assay for initiation will be used to clarify specific aspects of oral carcinogenesis, including: (1) the role of cell proliferation in the induction of initiated basal cells, (2) the ability of known or suspected carcinogens to induce initiated cells in oral mucosa, (3) the length of persistence of initiated cells, (4) the role of selective proliferation of initiated cells in the ultimate production of cancer, and (5) the response of initiated cells in oral mucosa to suspected promoting agents. Gamma glutamyltranspeptidase (GGT) activity will be monitored biochemically and histochemically, in whole buccal pouch and in individual mucosal lesions respectively, in order to assess the usefulness of this enzyme as a marker for oral neoplasia. Traditional histopathological criteria, GGT histochemical activity, and 3H-thymidine-autoradiography will be used to characterize the individual DMBA-induced mucosal lesions at successive stages of neoplastic development and to predict their biological behavior. In addition, the presumptive promoting agents, TPA, ethyl alcohol, and topical vitamin A, will be investigated for their ability to encourage the selective proliferation of putative initiation sites and to promote oral cancer development.

122. SQUAMOUS CELL CARCINOMA - INVASION MECHANISMS

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OBJECTIVE: The mechanism of invasion of squamous cell carcinoma into normal tissue and basal laminae will be examined (1) at the leading edge of tumor in human head and neck biopsies; (2) in carcinoma in situ in biopsies and exfoliated cells and in early skin cancer of mice; and (3) in an isogeneic organ culture invasion model system consisting of cultured adult mouse epithelium and added dissociated cells from skin tumors induced in the same promotion.

APPROACH: The biopsy material will be examined by thick-section stereoscopy using the Albany 1.2 MV High Voltage Electron Microscopy (HVEM) and light microscopic (LM) immunofluorescent staining of the tonofibril network. The kinetics of invasion in the model system will be quantitated in terms of the extent, depth and speed of invasion, invasive cell proliferation and dedifferentiation of the invasive cells. The extent of formation of the tonofibril network and its intracellular distribution will be examined by LM (Aniline Blue-Orange G-stain and immunofluorescence) and stereo HVEM both for motile-invaded cells and resting-invaded cells. Keratin synthesis will be modified by retinoids, protein synthesis inhibitors and hydrocortisone. The role of lysosomal enzyme release in invasion will be studied by stereo HVEM of acid phosphatase stained cells and by addition of proteases and protease inhibitors. The relation between invasion and cell proliferation will be studied by use of metabolic and microtubule inhibitors. At higher doses, chemotherapy agents will be used to search for selective toxicity for the invasive cells.

It is hoped that this work will suggest new modes of therapy for squamous cell carcinomas.

123. STABILITY OF DIFFERENTIATION - CRANIOFACIAL STUDY

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The aim of this research is to examine the maturational changes that occur in cultured epidermal and oral keratinocytes as they transit from the basal layer to the surface. We seek to learn how these changes are controlled in normal and pathologically altered epithelia. In the next year our experiments will focus upon three aspects of epithelial metabolism: 1. The regulation of keratin synthesis and tonofilament assembly in cultured keratinocytes from oral dysplastic and neoplastic lesions. 2. The fractionation of normal keratinocytes based upon their maturational age and an analysis of keratin biosynthesis in these fractions. 3. The effect of adenovirus infection upon the metabolism of cultured epidermal keratinocytes.

BIBLIOGRAPHIC REFERENCES: Taichman, L., Reilly, S. and Garant, P.R. (1979) In vitro cultivation of human oral keratinocytes. Archs. Oral Biol. 24:335-341. Taichman, Lorne, B. and Setlow, Richard, B. (1979) Repair of ultraviolet light damage to the DNA of cultured human epidermal keratinocytes and fibroblasts. J. Invest. Dermatol. 73:217-219.

B. CHARACTERIZATION OF TUMORS AND PRECANCEROUS LESIONS

124. SCLEROMA - ULTRASTRUCTURAL STUDY

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OBJECTIVE: To determine the ultrastructural characteristics of nasal scleroma.

MATERIAL: Material is obtained from biopsies of lesions with diagnosis of scleroma confirmed by light microscopy.

METHOD: Pre-fixation in glutaraldehyde, fixation in osmium tetroxide, inclusion in epon-araldite, impregnation with uranil acetate and lead citrate. Study by electron microscopy. (Translated)

125. KERATOHYALINE GRANULES IN ABORTIVE KERATINIZATION AND EPITHELIAL/CONNECTIVE INTERPHASE IN PATHOLOGICAL INDUCTION CONDITIONS

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The object of the study is to investigate the structure of keratohyaline granules in normally unkeratinized oral mucosa which has been exposed to chronic irritation. The epithelial layers of twenty specimens of leukoedema, leukoplakia and focal epithelial hyperplasia and 20 specimens of clinically normal mucosa will be compared ultrastructurally.

The object of the second study is to investigate the inductive changes at the epithelial connective tissue junction in tumors and cysts which show 'hyalinization' next to epithelium. Five examples will be investigated ultrastructurally.

126. ELECTRON HISTOCHEMICAL STUDY OF THE RELATIONSHIP BETWEEN TONOFILAMENTS AND DESMOSOMES IN ORAL PRECANCEROUS LESIONS - LEUKOPLAKIA

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OBJECTIVE AND APPROACH: Majority of the cases of oral precancerous lesion - leukoplakia - used tobacco either in the form of smoking or chewing or both. In the human oral buccal mucosa addicted to tobacco or in oral cancer or leukoplakia, dyskeratosis and presence of dense tonofibril bundles which fail to anchor on desmosomal attachments are commonly observed. The significance of this phenomenon is loss of intercellular communication with resultant loss of regulatory growth control. This investigation is proposed to evaluate how exactly the failure develops in contact areas between tonofilaments and desmosomes, using silver methanamine. Using the techniques proposed, in-depth elucidation of the keratinization aberrant to the human oral mucosa will also be possible. A number of biopsies of oral precancerous lesions will be studied using routine staining uranyl acetate and lead citrate and silver methanamine techniques in order to localize the prekeratin.

127. CHARACTERIZATION OF ORAL MUCOSA AND SKIN BASAL LAMINA

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The proposed research on the basal lamina (BL) of stratified squamous epithelium (SSE) involves the following: 1. Isolation of SSE-BL from human oral mucosa and skin using a variety of denaturing and reducing agents to accomplish selective solubilization. 2. Purification of the individual BL proteins using a combination of ion exchange chromatography, gel filtration and immunoadsorption. 3. Elucidation of the major chemical and physiocochemical properties of the purified proteins. 4. Immunological characterization of BL from bovine fetal calf and human skin using immunohistochemical, immunocytochemical, immunochemical and immunoelectrophoretic techniques. Immunological identity and cross-reaction with basal laminae from homologous and heterologous tissues and species will be determined. Ultrastructural localization of the antigenic determinants of BL will be established using immunoelectronmicroscopy with peroxidase and ferritin conjugated antibody. BL synthesis in healing wounds of the oral mucosa and skin will be studied by fluorescent antibody and immunoelectronmicroscopic techniques. 5. Investigation of BL changes in a group of diseases which manifest their pathology in the mucosa of the oral cavity, including: squamous cell carcinoma, bullous and benign mucous membrane pemphigoid and adenocystic carcinoma.

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128. BIOCHEMICAL PATHOLOGY OF MURINE POLYOMA TUMORS

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The first objective of this study is to isolate, purify, and characterize the factor(s) present in polyoma virus induced tumors of the mouse salivary gland which supports growth and morphogenesis of normal salivary epithelium. This will entail the development of an assay system utilizing the electrophoretic separation of tumor macromolecules and a variety of purification procedures: chromatography, salt precipitation, and preparative electrophoresis. Immunochemical techniques will be used in characterizing the factor(s).

The second objective of this project is to characterize tumors induced by polyoma virus in different organs with respect to their isozyme repertories for a wide range of enzymes, and to compare these patterns to the normal tissues from which the tumors were derived. Tumors not caused by polyoma virus will also be used as controls. Tumor-specific isozymes will be investigated as markers for tumor growth and/or regression.

129. ROLE OF THE REGIONAL LYMPH NODE IN ORAL NEOPLASIA

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The objective of this research proposal is to study the relative role of lymphocytes from regional and distant lymph nodes, spleen, and peripheral blood by means of in vitro cell-mediated reactivity to syngeneic rat oral tumors. A microcytotoxicity assay is being used to determine levels of in vitro cytotoxicity at various stages of tumor progression. Oral tumors induced by the chemical carcinogen dimethylbenzanthracene are being studied both in the primary host and in a transplantable tumor system. This study may provide a valuable model for the study of neoplasms of the oral cavity which may better clarify the roles of lymphocytes from various anatomical locations in the host defense mechanism against oral cancer.

III. PRECLINICAL DIAGNOSIS AND THERAPY

130. CHROMOSOMAL INDICATORS OF MALIGNANCY

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OBJECTIVE: By chromosome studies in solid tumors, as well as long-term cell cultures derived from solid tumors and from precancerous lesions, specific patterns of chromosome damage of malignant deterioration are investigated. Comparison of karyotypes from precancerous lesions and malignant tumors as well as from tumors and metastases and from direct preparations and derived cell cultures is expected to yield evidence on karyotype evolution in malignancy.

APPROACH: The studies are performed on excision material from surgical specimens of solid breast tumors as well as from precancerous lesions of the mouth epithelium. Material from other areas (e.g., colorectal carcinoma, neoplasias of the mouth and nasopharynx) will also be included in these studies.

PROGRESS: Since the studies were started in 1978 so far only technical problems of tumor cell culture and chromosome preparation from solid tumors have been handled. First observations on the existence of 'double minutes' also in solid breast tumors (not only in cultured cell lines) have been made. Further progress in evaluation of specific cytogenetic changes related to malignancy is expected as a result of the work of the next three years.

131. SALIVARY GLANDS, POLYAMINES AND CHEMOTHERAPY

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The possible involvement of polyamines in growth, differentiation and neoplasia has stimulated the study of endogenous levels of these compounds (putrescine, spermidine and spermine) and enzymes responsible for their synthesis (ornithine and S-adenosylmethionine decarboxylases). In particular, reports on increased polyamine levels in rapidly growing and neoplastic tissues have prompted a search both for techniques which might be used diagnostically to detect abnormal polyamine levels and for specific inhibitors of polyamine synthesis.

To date, little is known about the polyamines and their synthesizing enzymes in salivary glands or in saliva. In addition, there is little use of chemotherapy for salivary or oral neoplasias and as a result, little is known about specific cytotoxic drug effects in tissues of the oral cavity or salivary glands.

Polyamine and decarboxylase levels and ultrastructural (EM) characteristics will be studied using mouse salivary glands, both normal and those induced to grow by injecting the mouse with isoproterenol (IPR). IPR-induced salivary growth involves both hypertrophy and hyperplasia and is used as a model growth system. The effect of certain antineoplastic drugs on normal and IPR-induced salivary tissues will be studied by correlating the biochemical and ultrastructural characteristics described above. During the study, correlations will be made between the polyamine and decarboxylase levels in the glands, the state of growth of the glands, and the effects of cytotoxic drugs on both the biochemical parameters and the structure/function relationships as observed microscopically.

It is not known if human saliva contains polyamines or their synthesizing enzymes. Saliva will be analyzed to determine if it contains these components in measurable quantities. If present, studies will be performed to examine the feasibility of using such analyses as a diagnostic method for assessing salivary gland growth and/or function.

132. HETEROTRANSPLANTATION OF HUMAN HEAD AND NECK CANCER IN THE NUDE ATHYMIC MOUSE - A POTENTIAL MODEL FOR ANTI-CANCER DRUGS

Sneeuwloper, G., Snow, G. B., Veldhuizen, R., Universiteit van Amsterdam, Dept. of Experimental Medicine/Otolaryngology, *Spui 21, Amsterdam, Netherlands*

OBJECTIVE: Evaluation of the effects of cytotoxic drugs commonly used in treating head and neck cancer patients and screening of 'new' drugs in head and neck squamous cell carcinoma transplanted in athymic nude mice.

APPROACH: Transplantation of human head and neck cancer in nude athymic mice: When tumors in the mice reach a size of 100-150 mm3 cytotoxic drugs are administered according to various dose schedules. Tumor volume is used as a parameter of the antitumor effects; serial transplantations are carried out.

133. A STUDY OF THE COLONY-FORMING ABILITY OF HUMAN TUMOR CELLS OBTAINED FROM CLINICAL BIOPSIES

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A cloning assay has recently been described that shows considerable promise as a means of predicting the clinical sensitivity of a patient's tumor by prior screening of that patient's tumor cells against a range of anti-cancer agents in vitro (Salmon et al., New England Journal of Medicine, 1978, 298, 1213).

An ongoing assessment is being made of the feasibility of extending the application of a cloning assay (developed by Courtenay et al., British Journal of Cancer, 1978, 38, 77) to a number of other malignancies. Particular emphasis is being placed on colo-rectal, head and neck, bladder and childhood tumors in collaboration with several hospital units.

By virtue of this ability of tumor cells to clone selectively in soft agar, this procedure also holds promise as a means of establishing human tumor cell lines for in vitro chemosensitivity testing.

134. A PHARMACOLOGICAL INVESTIGATION OF LARREA DIVARICATA - ANTINEOPLASTIC PROPERTIES

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OBJECTIVE: Evaluate the antineoplastic properties of Larrea divaricata (creosote bush) towards a naturally occurring bovine neoplasm and two laboratory screens. Elucidate the active antineoplastic agent(s) present in Larrea divaricata and conduct preliminary structure activity investigations. Evaluate the mechanism of action of the elucidated antineoplastic agents by comparing their effects on normal and tumor cell metabolism.

APPROACH: Isolates from Larrea divaricata will be evaluated for their activity towards a naturally occurring bovine neoplasm (bovine eye carcinoma) and three laboratory screens, including the NIH KB cell culture screen, an appropriate microbiological bioassay, and an in vivo laboratory animal screen (leukemia L-1210 or Sarcoma S-180). The screening tests will be employed to assist in the elucidation and purification of the 'active' antineoplastic principle(s) in Larrea divaricata. Any active anticancer compounds will be tested in the bovine eye carcinoma clinical trials. In addition, we propose to investigate the mechanism of action of any new antineoplastic agents that are elucidated by the screening tests listed above by comparing the effects of the various antineoplastic agents on normal and tumor metabolic processes that are fundamental in supporting life.

PROGRESS: We conducted a clinical trial employing crude extracts of Larrea and observed a dramatic regression of bovine ocular squamous cell carcinoma. This cow has been in total remission for three months. We have maintained a complete set of gross photographs for future publication. We initiated a structure-inhibition study on a series of 17 flavones in both the respiratory chain and ATPase components in mitochondria. NADH oxidase activity was more sensitive to the flavones than succin-oxidase. Fisetin and quercetin were the only effective inhibitors of succin-oxidase. The relative potency in the NADH oxidase system were fisetin greater than quercetin greater than chrysin greater than flavone greater than flavanone greater than genistein greater than morin approximately perspective to 5-OH-flavone greater than apigenin. At a single high dose of 800-1000 nMoles/mg protein, all flavones tested inhibited oligomycin sensitive ATPase. We determined the hydroxy and methoxy configurations of the model phenolic compounds. (Text Abridged).

135. ORAL CARCINOGENESIS, VITAMIN A AND RETINOIDS

Shklar, G., Kornhauser, A., Solt, D. B., Harvard University, Boston Campus, Harvard School of Dental Medicine, Dept. of Oral Medicine & Oral Pathology, *188 Longwood Ave., Boston, Massachusetts*, 02115, United States of America

The specific aims of this project are to determine whether vitamin A or the synthetic retinoids administered systemically can act to delay or inhibit carcinogenesis of oral mucous membrane. Two well established oral mucosal tumor systems will be used: the hamster buccal pouch epidermoid carcinoma induced by DMBA in oil and the hamster tongue epidermoid carcinoma induced by DMBA in acetone. Delayed carcinogenesis will be evaluated histologically by delayed appearance of dysplasia, carcinoma in situ and frank invasive epidermoid carcinoma. Retinoids studied will be vitamin A, retinyl acetate, retinyl palmitate, and 13-cis-retinoic acid. The presence of retinoids in the oral mucosa, dysplastic oral epithelium and carcinoma will be studied by autoradiographic techniques and by chemical techniques. Aryl hydrocarbon hydroxylase activity of tissues will also be studied.

136. FLOW CYTOMETRY OF CELL POPULATIONS FROM HUMAN AND EXPERIMENTAL TUMORS (IMPLICATIONS FOR RADIOBIOLOGY AS APPLIED TO RADIOTHERAPY)

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OBJECTIVE: In clinical practice, resistance to treatment is a strictly empirical concept, based only on the operational response of a tumor to radiation treatment. The increasing availability of multimodality treatment approaches calls for the identification of parameters useful in predicting tumor (radio)resistance.

APPROACH: In a search for such parameter(s), flow cytometry (Phywe apparatus) methods are being employed in order to test the hypothesis that a tumor can be expected to respond poorly according to some cellular characteristics. This approach has been tested on a radioresistant murine sarcoma and on biopsy samples from head and neck cancer patients. The preliminary observations indicate that clinical radioresistance should be expected if: (1) the tumor is characterized by a multiple cell population in terms of DNA content; (2) a relatively high fraction of supposedly nonproliferating cells is present.

The same approach is being used also in an attempt to obtain information on other diagnostic and prognostic features of malignant tumors such as the degree of malignancy or aggressiveness and the metastic behavior.

PROGRESS: Flow cytometry can be a useful tool in clinical oncology, especially in the optimization of treatment of resistant tumors. The application of this method may depend upon the degree of cooperation between basic scientists and clinicians in the correct interpretation of a large amount of quantitative data. The sophistication of this kind of apparatus calls for an interdisciplinary effort, especially in regard to the development of data analysis systems.

137. INTENSIVE TREATMENT OF RETINOBLASTOMA

Schipper, J., Lagendijk, J. J., Tan, K. W., Rutgers, D. H., Academic Hospital, Dept. of Radiotherapy, *Catharijnesingel 101, Utrecht, Netherlands*

OBJECTIVE: Improvement of the results of the conservative treatment of retinoblastoma by: 1) optimalization and improvement of the irradiation techniques and 2) combination of radiotherapy with hyperthermia.

APPROACH: 1) Development of an accurate irradiation technique for retinoblastoma. 2) Evaluation of visual results and ocular complications following radiotherapy for retinoblastoma. 3) Treatment of retinoblastoma with radiotherapy combined with hyperthermia: a) development of a computer-controlled microwave heating technique for local hyperthermia of the posterior half of an affected eye; b) development of a temperature measuring technique for determination of the temperature in and around the eye without disturbing the microwave field and the heat distribution; c) determination of temperature distributions in the rabbit eye with or without microwave heating and correlation of the results with a mathematical model; d) study of the damage to the rabbit eye (particularly the lens) after radiotherapy, microwave hyperthermia, or a combination of both; e) study of the effect of radiotherapy combined (or not) with microwave hyperthermia on retinoblastoma implanted in the anterior chamber of the eye in nude mice; f) study of the effect of radiotherapy combined with hyperthermia on the cell kinetics of retinoblastoma in the above-mentioned model, with flow cytofluorometry.

138. FATE OF CAROTID ARTERY AFTER RADIOACTIVE IMPLANTS

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Considering that radioactive interstitial implants (brachytherapy) are assuming an increasing role in cancer therapy, their effects on normal tissues are not as well understood as they ought to be. Iodine-125 and Iridium-192 are two radionuclides utilized for head and neck cancer therapy and for therapy of other sites and produce very high local tumor control rates. Since primary or recurrent tumors involving the carotid artery present such a formidable challenge, it is natural that interstitial implant techniques have been adopted to produce cures in humans. This project seeks to determine the safety of interstitial implants in the carotid artery in different situations simulating human presentations.

Dogs will undergo surgery simulating the defect produced by a radical neck dissection and then the carotid artery will be implanted with either Iodine-125 (7,500-30,000 rad) or Iridium-192 (3,000-12,000 rad). Baseline and follow-up angiography will be done to determine the functional outcome and correlated with necropsy findings at one year. Three other conditions simulating commonly encountered human presentations will be studied. The results should have application in the preparation of implants used for other sites.

Data analysis will be performed via the Stanford Center for Information Processing IBM/30/168 computer utilizing the program language SPSS, version 7.2.

139. PROTECTION OF THE PAROTID GLAND FROM RADIATION DAMAGE DURING RADIOTHERAPY

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Tumors of the head and neck are particularly destructive, debilitating and difficult to deal with. Surgery alone is a particularly destructive treatment; in combination with chemo- and radiotherapy surgery is made less radical. Radiotherapy attempts eradication of the neoplasm by irradiating to the limits of tolerance. However, normal tissues, contiguous to the tumor, which need to be freed of tumor microfoci or through which the irradiation must pass, suffer trauma and disruption, resulting in mucositis, sialadenitis, xerostomia, radiation caries, and osteomyelitis.

Because radiation therapy relies upon the often small margin of differential radiosensitivity between normal and malignant tissue, the radiation dose delivered must be carefully balanced to destroy all malignant cells while sparing the surrounding normal tissue. The present study in rodents is an attempt to widen the differences in sensitivities of salivary glands and their neoplasms by using a radioprotector (WR-2721) in order to spare the normal parotid gland and a radiosensitizer (Ro-07-0582) to more effectively irradicate a salivary gland malignancy. The project will study the protecting and sensitizing properties of both compounds, independently at first and then together, upon normal and malignant tissues in the hope that the two compounds, simultaneously administered, can widen the radiosensitivities and so enhance the therapeutic index and the efficacy of radiation therapy.

The study is also probing the possibility of utilizing other, already available drugs which have already shown preliminary promise and have in common secretion-inducing properties, e.g., isoproterenol, as a possible substitute for the still experimental radioprotector, WR-2721. In addition we will investigate cAMP as a chemoradioprotector and as the induced intracellular compound conferring the protection.

Finally, should other effective protectors of normal tissue be found we will test their compatibility with the tumor radiosensitizer Ro-07-0582.

140. RADIATION THERAPY AND BIOLOGY RESEARCH PROGRAM

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Clinical studies in advanced carcinoma of the head and neck region, Hodgkin's disease and non-Hodgkin's lymphomas, carcinoma of the breast, gastrointestinal cancer, gynecologic malignancies, prostatic cancer and radiation dose rate effects on the hematopoietic system are continued and new studies are planned.

Radiological physics research includes: magnetic control of the dose distributions produced by high energy electron beams, calorimetric determination of dosimetric parameters and general medical physics.

Laboratory investigations include: experimental radiation therapy of rodent solid tumors, radiation reaction preventive agents and normal tissue response, the response of vascular endothelium to ionizing radiation, NMR detection of hypoxic cells, the influence of the red blood cell concentration of 2,3-diphosphoglycerate on the radiation response of the rat rhabdomyosarcoma R1112.

Our investigations also include: enzymatic mechanisms in postreplication repair; study of error-prone DNA repair pathways in mammalian cells, study of herpes virus genome structure, site specific mutagenesis in gene for thymidine kinase of herpes simplex virus; molecular mechanisms of DNA repair in E. coli, hypoxic radiosensitizers: structure-function relations and mechanisms of sensitization and toxicity; analysis of gene function involved in genetic recombination in E. coli; site directed mutagenesis, role of secondary structure in gene regulation; cell proliferation in EMT6 tumors and examination of new agents for altering the radiation response of solid tumors.

141. IMMUNOCOMPETENCE OF CANCER PATIENTS

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The overall objectives of this proposal are to evaluate the non-tumor-specific immune reactivity of cancer patients in order to determine the effect of malignancy itself and cancer therapy upon the patients' immune resistance. A major portion of this proposal has focused on the macrophage and PMN. A reliable method of obtaining the human macrophage has been developed and we are continuing to investigate the effect of neoplasia and cancer therapy upon macrophage and polymorphonuclear leukocyte function, and the relationship of the macrophage and PMN to effector lymphocytes, and are seeking to determine the effect of non-specific immunologic stimulants, such as BCG and interferon on macrophage and PMN functions.

Methodologies to be employed are as follows: Macrophage and PMN cytotoxicity, subcelluler fractionations and in vivo models utilizing immunosuppressed hamsters.

We have previously learned from this project that there is an immune deficit associated with progressive neoplasia. Our results indicate that there is an excellent correlation between DCHR and DNCB and the clinical extent of malignancy. In vitro results indicate that PMNs such as lymphocytes and macrophages can selectively destroy tumor cells both in vitro and in vivo. Continued efforts in purification of isolated PMN cytoxic factors are underway.

This program is highly relevant to the treatment of patients, since a clearer insight into the mechanism of tumor cell destruction by the macrophage and PMN may lead to a better understanding of immune reactivity to tumor cells and thus a more effective means of treatment of human neoplasia may be possible.

142. CIG FUNCTION - INTERACTION WITH FREE MACROPHAGES

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Previous studies of cold insoluble globulin (CIG) have directly or indirectly associated its opsonic activity with the function of the sessile macrophages of the reticuloendothelial system (RES), particularly with the Kupffer cells of liver. The research described herein examines the role of CIG in aiding macrophages to carry out those functions, normally performed only by nonsessile macrophages, e.g. the cytostasis and/or cytotoxicity of peripheral malignant cells or the removal of cell debris as part of the normal wound healing process. A model system developed in this laboratory will be used to determine the characteristics of CIG interactions with both macrophages and target particles including sickled erythrocytes and tumor cells in culture. Studies using standard assays for cytostasis and cytotoxicity of cultured neoplastic cell lines, with/without added macrophages and CIG, will be performed to determine if CIG acts directly, or in conjunction with macrophages, to express these functions. The in vivo effect of elevated or depressed levels of CIG on metastasis rate will also be determined using a mouse salivary gland carcinoma model system. Using appropriate counting and microscopic techniques with 125I, fluorescein or ferritin labeled CIG, the binding of CIG to cellular debris in vivo and in vitro will be studied. The interaction of macrophages with the CIG-cell debris complex in clearing the wound will also be characterized. Both experimentally produced injuries and the 'natural,' chronic ulcers of patients with sickle cell anemia will be studied. The therapeutic use of CIG in the treatment of these chronic ulcers and patients with extensive burns will also be determined. Further studies will examine the sequestration of CIG at the site of an injury in patients who have undergone radical mastectomy.

143. COLLAGENASE AND INVASION OF HEAD AND NECK TUMORS

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The objective of this project is to analyze and characterize a collagenolytic enzyme from a variety of head and neck tumors and to determine the significance of collagenolysis in the invasiveness and clinical behavior of these malignancies in humans and in an experimental epidermoid tumor in rats.

The current research was to compare the levels of collagenase and protease activities according to the anatomic site, histological pattern (i.e., squamous versus nonsquamous), tumor size and tumor differentiation. We have also studied the effect of prostaglandin (possibly a chemical mediator for tumor growth and spread) on the synthesis and the release of collagenase and protease. The animal model also will be used to study immunoinhibition of collagenase in vitro and in vivo to test whether immunoinhibition of collagenase will decrease tumor invasiveness and improve animal survival.

We hope that as a result of these studies, a treatment plan for head and neck tumors can be placed on a more rational basis.

BIBLIOGRAPHIC REFERENCES: Huang, C.C., Wu, C.H., and Abramson, M.: Collagenase Activity in Cultures of Rat Prostate Carcinoma. Bioch. Biophys. Acta 570:149-156, 1979.

144. STUDIES IN TECHNIQUES AND APPLICATION OF MICROVASCULAR RECONSTRUCTIVE SURGERY

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OBJECTIVES: To allow residents access to the laboratory to practice microsurgical techniques and to study the potential applications of microsurgical techniques in experimental animals prior to these procedures being performed in patients.

PLAN: Rats are available for microsurgical procedures. One to two weeks after operation, the rats are re-explored to assess the patency of the anastomoses. A project to replace the esophagus with jejunum is in progress. The plan was to develop techniques to facilitate the use in hypopharyngeal and esophageal replacement or reconstruction in head and neck cancer patients. The intrinsic contractility and histologic appearance of the bowel after transfer was to be determined. Also manometric studies to ascertain contractility were to be performed.

METHODOLOGY: Standard microvascular techniques are used for the rat anastomoses. Microsurgical sutures of 10-0 nylon and prolene are available. Resection of the cervical esophagus in a dog is performed. A portion of jejunum is isolated on vascular pedicle. The isolated segment of bowel is brought into the neck and anastomosed to the branch of the carotid artery and internal jugular vein. The cervical esophageal and hypopharyngeal defect is closed with jejunum.

FINDINGS: There is no definitive data on the results on the rat femoral vessel anastomoses. To date four animals have had jejunal transfers. Manometric studies have been done. The dogs are now receiving postoperative radiotherapy. They will be evaluated further.

145. EXTENDED ORBITAL RESECTION

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Current practice provides certain accepted forms of management for carcinoma of the paranasal sinuses. Critical review of maxillectomy reveals that standard orbital exenteration adds little to the ultimate control of tumor. The addition of transcranial resection of the cribriform plate has improved survival according to Ketcham.

It is the intent of this project to consider a wider field of excision in hopes of providing further improvement in local tumor control rates.

The project will consist of three sections: (1) Osteology: dissection of human skulls to consider bony anatomy. (2) Soft tissues: dissection of human cadaver heads to consider relevant neural and vascular anatomy. (3) Live animal: wide-field resection of bony orbit on experimental animal (cat) to evaluate applicability of procedure.

Should the project result in a positive impetus, a supplemental project is intended. The live animal procedure would be repeated with the addition of pre-operative irradiation.

146. CRYOGENIC PHYSIOPATHOLOGY AS RELATED TO CANCER THERAPY

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PROJECT OBJECTIVES: To determine: (1) If tissue sites of cryosurgery attract and retain circulating oncocidal drugs, and the influence of time-dose-route variations. (2) Possible relationships of drug concentration gradients and post-freeze local vascular changes. (3) If oncolytic cryosurgery of bowel and/or liver can be feasibly combined with chemotherapy.

RESEARCH PLAN: (1) Serial sections of tissue of rabbits, mice, and tumor-bearing mice treated with cryosurgery and infused with 5-fluor (6-3H) uracil are tested for drug concentrations by scintillation counting and autoradiography. (2) Gradients are related to vascular changes by microangiography of serial sections of barium-infused specimens. (3) Survival rate, autopsy, and blood analysis are used to evaluate the safety of combined cryosurgery and drug therapy in the dog.

METHODOLOGY: Liquid nitrogen probes, parenterally injected drugs, frozen section autoradiography, liquid scintillation counting, infusion microangiography, and surgically isolated frozen bowel segments are being used. Studies involve rabbits, C3H tumor bearing mice and dogs.

FINDINGS: (1) 5-FU concentrates in rabbit and mouse tissues peripheral to cryolesions. (2) Higher peak zonal differentials of isotope can be shown in mice, facilitating autoradiography. (3) Microangiography of 48 hour cryolesions in rabbits show vascular shunting and dilitation. (4) Bowel cryosurgery plus methotrexate (5 mg/kg) was tested successfully in four additional dogs (cumulative series of eight).

CLINICAL RELATIONSHIP: Clinically observed oncolytic enhancement of combined cryosurgery/chemotherapy presaged need for drug/histo-physiologic data base to guide human trials in quest for better methods for control of oral and bowel cancer.

IV. CLINICAL DIAGNOSIS AND PROGNOSIS

A. HISTOLOGICAL METHODS

147. METHODS OF EARLY DIAGNOSIS OF CANCER OF THE MOUTH

Ribeiro de Almeida, C. I., Lima, R., Cretella, P. R., Faculdade de Medicina de Jundiai, *Rua Francisco Teles 250, Jundiai 13200, Brazil*

OBJECTIVE: To verify the effectiveness of non-traumatic, innocuous and simple techniques that could be used on a large scale in out-patient clinics for the early diagnosis and prevention of cancer of the mouth.

APPROACH: Select 40 mouth lesions including white, ulcerative and tumorous lesions. Perform Papanicolaou test, staining with orthotoluidine blue, photography before and after staining, and conduct a biopsy and anatomicopathologic examination of the lesion. Once these data are obtained the findings will be compared in order to determine the efficiency of the Papanicolaou test and ortholouidine blue stain in distinguishing between benign lesions and those of varying degrees of dysplasia. (Translated)

148. STUDIES OF NASAL CANCER IN WORKERS EXPOSED TO NICKEL AND DEVELOPMENT OF METHODS FOR SCREENING AND EARLY DIAGNOSIS (ABBREV)

Boysen, M. E., Reith, A. K., Norsk Hydro's Inst. for Cancer Research, Laboratory of Electron Microscopy, *Montebello, Oslo 3, Norway*

The summary for this project is under entry no. 108.

149. DIAGNOSIS OF INTRACRANIAL TUMORS BY CYTOLOGY OF CEREBROSPINAL FLUID

Parulkar, G. B., Chitale, A. R., Nagpal, R. D., Gandhi, V. A., King Edward VII Memorial Hospital, Dept. of Surgery, *Parel 400012, Bombay, India*

OBJECTIVE: To study cerebrospinal fluids cytologically for space-occupying lesions.

APPROACH: The cerebrospinal fluids obtained by ventricular and lumbar puncture were examined during a period of 6 months. Cystic fluids were also included in this study. Smears were prepared, stained by hematoxylin-eosin method and the results reported immediately. Excluding the unsatisfactory preparations, the accuracy rate assessed in 150 cases was 92%.

150. MASSIVE DETECTION OF ORAL AND MAXILLOFACIAL CANCER

Lobos, N. J., PLAPO, *Jose Miguel de la Barra 475, Casilla 1903 - Correo Central, Santiago, Chile*

OBJECTIVES: 1. To detect oral and maxillofacial malignant and pre-malignant lesions in the population of the metropolitan area of Santiago, Chile; 2. To put into operation a service for early diagnosis; 3. To offer these services to the public; 4. To evaluate the diagnostic methods used; 5. To obtain prevalence and incidence rates for these lesions; 6. To teach pregraduate students at the Faculty of Odontology; 7. To register and follow-up detected cases; to refer patients to the appropriate treatment centers.

METHOD: 1. Promotion of self-examination of the oral cavity in the public; 2. Clinical examination; photography; toluidine-blue test; exfoliative cytology (specimen collection, processing and diagnosis of slides) and biopsy of suspicious lesions; 3. Tabulation and evaluation of results according to the International Classification of Diseases-Oncology.

151. DIAGNOSTIC CRITERIA AND TECHNIQUES FOR DETECTION OF ASYMPTOMATIC ORAL CARCINOMA - IDENTIFICATION OF HIGH-RISK GROUPS

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It appears that erythroplastic portions of asymptomatic oral squamous cell carcinoma stain positive with toluidine blue. Very few false positives are found if toluidine blue is used in conjunction with previously defined clinical criteria (erythroplasia). Suspicious oral lesions found during routine oral examinations are referred to the investigator. Lesions which persist for 10-14 days are described, photographed, and a demographic questionnaire is completed by a trained interviewer. A clinical diagnosis is made and the lesion is stained using toluidine blue. Results are recorded. A biopsy renders final pathological diagnosis. Demographic data are being evaluated to delineate what percentage of these patients with oral squamous cell carcinoma drink or smoke heavily, have developed or have had other primaries of the upper aerodigestive tract, including the mouth. It should be noted that these are for the most part independent squamous lesions. Additionally, recurrence and survival rate for patients with early asymptomatic lesions is being studied. A control group is also being studied. All admissions to the hospital have a scheduled appointment for oral examination in the Dental Clinic. Patients scheduled each day (over 40 years of age) are interviewed and questioned. The only bias in selection is that patients who are too ill to attend the clinic are not taken or that patients are inadvertently missed for interview. Since the patients with early erythroplastic oral cancer are those who are examined in the same way, the controls are in the same population.

152. DIAGNOSTIC AND PROGNOSTIC INDICATORS IN ORAL DYSPLASIA AND MALIGNANCY

Johnson, N. W., Evans, S., Morgan, P. R., University of London, London Hospital Medical College, Dept. of Oral Pathology, *Turner St., London E1 2AD, England, United Kingdom*

OBJECTIVE: Histological studies of cases of human oral cancer with a follow-up period of at least 5 years have shown previously that the host immune-inflammatory response is as important as epithelial features in predicting survival. Further analysis of the data has been carried out by a statistical method (Cox, 1972) which can be applied to surviving patients and which corrects for the effect of age on survival. These results showed an even higher correlation of intensity of host response with poorer prognosis.

APPROACH: Loss of blood group antigen and acquisition of actin as shown by immunofluorescence have been demonstrated in oral cancer and in moderate/severe oral epithelial dysplasia. Present studies aim to correlate these features with ultrastructural changes in closely corresponding regions. Controls consist of normal, hyperplastic and migrating (wound healing) oral epithelium. (Ref. Cox, D.R. and J. Roy., Statis. Soc. (B) 34, 187-220, 1972.)

153. DIAGNOSTIC AND PROGNOSTIC FEATURES IN THE HISTOPATHOLOGY OF ORAL MALIGNANT AND PREMALIGNANT MUCOSAL LESIONS

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The aims of the study are to determine which clinical and histopathological features of oral cancer have diagnostic and prognostic value. A range of clinical and microscopic features (23 related to the epithelium and 16 related to connective tissue) has been scored from 100 cases with at least 5-year follow-up, using specially devised semiquantitative scales, and analyzed for correlation with patient survival and behavior of the tumor, using a computer. The work is continuing but preliminary results indicate that host immune inflammatory response as seen in tumor stroma is at least as important as epithelial features in predicting survival. Factors such as mitotic activity and degree of keratinization, traditionally given great weight in grading epithelial neoplasms, do not appear to be of great prognostic value.

154. HISTOMORPHOLOGIC STUDY OF BUCCAL CARCINOMA

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OBJECTIVE: To determine the histomorphologic and enzymatic characteristics of buccal carcinoma, comparing them with prognosis and clinical course.

METHOD: Topographical and anatomoclinical classification of carcinoma of the buccal mucoca, with particular emphasis on clinical stage; histomorphologic classification; enzymatic and classic histochemical study of histologic variations. Comparison of these findings with the capacity for dissemination and the prognostic and clinical evolution to a determined and close stage.

PROGRESS: Determination of the normal histochemical patterns of buccal mucosa and development of the techniques to be used.

155. PROGNOSTIC FEATURES IN THE HISTOPATHOLOGY OF ORAL SQUAMOUS CELL CARCINOMA

Johnson, N. W., Hopps, R. M., Evans, S., Yip, W. K., University of London, London Hospital Medical College, Dept. of Oral Pathology, *Turner St., London E1 2AD, England, United Kingdom*

This study is designed to seek correlations between clinical and histopathological features and the prognosis of patients with squamous carcinoma of the oral mucous membrane. A wide range of histological features is scored from sections of the original diagnostic biopsy on a semi-quantitative basis. These include features of both the epithelium and the tumor stroma.

Data are analyzed using the statistical package for the social sciences with corrections for age employing both the Peto and Peto method and the Cox method.

Preliminary data indicate that many variables traditionally regarded as of importance, such as mitotic activity, do not by themselves strongly influence survival. Among the epithelial features, the diffuseness of the infiltration pattern is the strongest unfavorable prognostic sign. Amongst connective tissue features, the density of immune inflammatory infiltrate is positively correlated with survival.

156. FLOW CYTOMETRIC DNA ANALYSIS OF HUMAN TUMORS

Vindeløv, L. L., Spang Thomsen, M., Engelholm, S. A., Finseninstitutet, Dept. of Internal Medicine, *49 Strandboulevarden, DK2100 Copenhagen, Denmark*

OBJECTIVE: Flow cytometric DNA analysis yields information on ploidy and proliferative characteristics of a cell population. By sequential analysis of treatment-perturbed cell populations, further cell kinetic information can be obtained. The objective of the project is to assess the value of DNA analysis for the subclassification of tumors and for treatment schedule design.

APPROACH: The DNA analysis is performed on fine-needle aspirates of human breast cancer, lung cancer, lymphomas, bladder cancer and cancer of the oral cavity.

PROGRESS: The results show a wide range of the pretreatment characteristics. Clonal heterogeneity has been demonstrated in small cell carcinoma of the lung and in breast cancer. The treatment kinetics of small cell carcinoma of the lung have been described and a treatment protocol based on the cell kinetic changes designed.

157. STUDY OF HEAD AND NECK CANCER BY SERIAL SECTION

Kirchner, J. A., Yale University, School of Medicine, Dept. of Surgery, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

OBJECTIVES: To improve present methods of preserving the functions of the larynx, pharynx and oral cavity when these organs must be treated for cancer.

APPROACH: Each surgical specimen removed for cancer of the larynx or hypopharynx, whether partial or total laryngectomy, is fixed in formalin, decalcified in nitric acid, dehydrated, and then processed through celloidin for whole-organ study by sections at 20 microns. Every 25th section is stained and mounted. The remaining sections are kept in serial order for later evaluation.

PROGRESS: This project has resulted in 21 publications describing patterns of growth and spread of cancer within the larynx and to surrounding structures. Current studies include a correlation of horizontal serial sections of the larynx with preoperative CT scan.

B. BIOCHEMICAL AND IMMUNOLOGICAL METHODS

158. BIOCHEMICAL AND IMMUNOLOGICAL MARKERS OF DIAGNOSTIC AND PROGNOSTIC IMPORTANCE IN ORAL CANCER

Shirodkar, S. R., Ghanekar, S. N., Vaidya, S. G., Harinath, B. C., G.M. Hospital & Research Inst., Laboratories of Biochemistry & Immunology, *E. Borges Rd., Dona Paula, Ilhas, Goa 403004, India*

About 40% of the cancer cases detected and treated in Gosalia Memorial Hospital run by the Goa Cancer Society, are cancers of buccal cavity, pharynx and larynx. Leukocyte adherence inhibition assay was shown to be useful in detection of cancer. An extensive study is planned to search for biochemical and immunological markers of diagnostic and prognostic importance in oral cancer. Enzymes such as amylase, G-6-phosphate dehydrogenase, lactic dehydrogenase, phosphohexose isomerase, alkaline phosphatare and their isoenzymes, ectopic hormones such as human chorionic gonadotropin and human placental lactogen and immunological marker carcinoembryonic antigen will be measured in saliva, serum and urine of oral cancer patients. In addition, leukocyte adherence inhibition assay will be done before and after treatment.

BIBLIOGRAPHIC REFERENCES: Use of leukocyte adherence inhibition test to study the cell mediated antitumor immunity in cancer patients. S.R. Shirodkar and S.G. Gangal. Ind. J. Med. Res. 70, 88-96 (1979).

159. ASSAY AND STRUCTURE OF CARCINOEMBRYONIC ANTIGENS

Todd, C. W., Shively, J. E., Clark, B. R., Pande, H., Gibson, D., City of Hope Medical Center, Division of Immunology, *1500 E. Duarte Rd., Duarte, California*, 91010, United States of America

The primary objective of this research has been to perform structural studies on carcinoembryonic antigen (CEA) and CEA-related antigens (TEX, NCA) in order to develop more specific immunoassays for the early detection of cancer and monitoring the progress of various types of cancer. Emphasis in the coming year will focus on microsequencing of peptide fragments from CEA and TEX formed by specific cleavages at methionine, tryptophan, lysine, and argine peptide bonds. NH2-terminal sequence information will be used to construct DNA probes which will serve as primers for enriching the specific synthesis of cDNA corresponding to CEA mRNA from various cell lines, and as screening agents for the isolation of recombinant DNA containing CEA cDNA. Work on the improvement of CEA immunoassays will focus on the use of monoclonal reagents in enzyme linked immunoassays (ELISA). A pilot study on the comparative use of CEA and TEX radioimmunoassays for serially monitoring cancer patients was recently completed. Expansion of these studies to a larger trial in breast cancer and head and neck cancer is under consideration.

160. DETECTION OF REACTIVITY TO TUMOR ANTIGENS IN CANCER PATIENTS

Vetto, R. M., Burger, D. R., Vandenbark, A. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Surgical Service, *Sam Jackson Park Rd., Portland, Oregon*, 97207, United States of America

Two tests to detect specific tumor immunity have been developed to measure reactivity to tumor extracts in patients with various stages of cancer undergoing conventional and instructional immunotherapy. The leukocyte adherence inhibition (LAI) test has been used to assess reactivity to melanoma, squamous cell carcinoma, colon adenocarcinoma, breast carcinoma and lung carcinoma extracts in 170 patient with a variety of tumors. There is a large variation in the discriminative ability of various extracts to distinguish patients in appropriate tumor groupings. In general, however, a higher percentage of patients with a given tumor respond to the extract of their own tumor type than controls at optimal extract concentrations. The antigen binding cell assay developed in this laboratory has also been effective in assessing tumor reactive cells in cancer patients. Patients with squamous cell carcinoma of the head and neck have ABCs to squamous but not to melanoma tumor antigens. These specific tumor antigen binding cells have been isolated and partially characterized. They appear to be cells from the macrophage-monocyte phagocytic series which have bound Ig via Fc receptors. Cell populations which have been depleted of monocytes or which have been blocked with anti-Ig fail to bind tumor specific or conventional antigens. These investigators have observed that patients with advanced, recurrent disease have lower frequencies of ABCs to squamous cell antigens than do newly diagnosed patients with primary malignancy or patients with different tumors.

161. DETECTION OF SERUM ANTIBODIES REACTIVE WITH ORAL TUMOR ANTIGENS

Winters, W. D., McAnear, J. T., Guest, G. F., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Dental Service, *San Antonio, Texas,* 78284, United States of America

During the period since the last report, we have continued to collect specimens and have attempted to grow them in tissue culture. The success rate for developing cell strains and cell lines from these patient specimens has been very low due to heavy infections of the specimen materials with bacterial and viral organisms residing in the oral cavity of the patients. We will be continuing our attempts at antigen purification and in vitro cell cultures, both of which should lead up to our goals of developing diagnostic and prognostic tests for serological analysis of patients with oral tumors.

162. ORAL IMMUNOPATHOLOGY - ORAL SQUAMOUS CELL CARCINOMA

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The aim of this proposal is to investigate some aspects of immunological approaches to the cancer of the mouth, pharynx and larynx. Using the squamous cell carcinoma (SCC) of the oral cavity as a model, we will make every effort to develop highly specific antibodies directed against squamous cell carcinoma antigens (SCCA) and to isolate highly purified SCCA. Our approach will be to construct monoclonal antibody secreting hybrid cells by fusing murine myeloma cells with spleen cells obtained from mice immunized with whole SCC cells or with semi-purified SCCA isolated from SCC cells by classical methods of membrane solubilization followed by protein separations. Monoclonal antibodies will then be coupled to insoluble support and will be used as immunoadsorbents to isolate highly purified SCCA. Once monoclonal antibodies and SCCA are available, we will use them in sensitive radioimmunoassays to detect SCCA and/or anti-SCCA antibodies in the sera of patients with SCC, versus the sera of patients with no tumor or with a tumor different from SCC. We hope to be able to correlate the presence of SCCA and/or anti-SCCA antibodies with the presence of the disease and therefore to be able to use this test for an early diagnosis of this cancer which is the most common tumor found in the upper respiratory tract. We will also use the monoclonal ant-SCCA antibody and the purified SCC in in vitro correlates of delayed cutaneous hypersensitivity (i.e., leukocyte migration inhibition, leukocyte adherence inhibition, lymphoblastogenesis) to evaluate the immunological responses of the tumor bearing patients to their autologous purified SCCA. We will look for a correlation between the magnitude of these responses and the stage of the disease in an attempt to evaluate the prognostic value of the tests described above as well as to possibly assess their usefulness in the evaluation of the efficacy of therapy and in the detectiion of recurrences after conventional therapy.

163. DEVELOPMENT OF IMMUNODIAGNOSTIC TESTS FOR CANCER

Ibrahim, A. N., Georgia State University, School of Arts & Sciences, Dept. of Biology, *33 Gilmer St. S.E., Atlanta, Georgia,* 30303, United States of America

OBJECTIVES: Increase the specificity and the sensitivity of an immunodiagnostic test for cervical and head and neck cancer. Purify the tumor associated antigens. Prepare specific antisera against these untigens. Periodically monitor the test by testing aliquots of sera from the same serum panel provided by NCI. An appropriate clinical evaluation of the immunodiagnostic test shall be done when the test is refined to the satisfaction of the Immunodiagnosis Program.

164. INTERDISCIPLINARY STUDIES ON NASOPHARYNGEAL CARCINOMA AND ASSOCIATED HUMAN TUMORS

De The, G., Cachin, Y., Sancho Garnier, H., Micheau, C., Ellouz, R., Cammoun, N., Ho, J. H., Molinari, R., Centre National de la Recherche Scientifique, Epidemiologie & Immunovirologie des Tumeurs, Fac. de Med. Alexis Carrel, *Rue G. Paradin, Lyon, France*

The objective of the study is to determine the importance of Epstein-Barr virus immuno-virological tests for clinical management of nasopharyngeal carcinoma. The specific aims are to evaluate IgA antibodies to EBV in serum and saliva of NPC patients as a marker for prognosis; to evaluate EBV serology and EBV markers in tumor cells as a complement to pathology to characterize malignancies arising in the nasopharynx, and to evaluate EBV serology as a tool for diagnosis in metastatic cervical lymph nodes with occult primary, and as a method of early detection in areas having a high incidence of NPC. The project will involve the following closely linked sub-projects: (1) a prospective study involving all new NPC patients in Paris, Milan, Tunis and most of the patients in Hong Kong, aimed at assessing the value of EBV immunovirology in the management of NPC using clinical, pathological and experimental parameters for the evaluation of survival at three and five years after diagnosis; (2) a case-control study involving different types of tumor arising in the nasopharynx as well as in the rest of the upper respiratory tract, with the aim of assessing the strength of the association between EBV and these tumors. This will include comparison of clinical, histopathological, epidemiological and experimental data on the different types of tumors observed; (3) a sub-study in Western European centers and in Tunis to assess EBV serology as a diagnostic tool to detect NPC in patients with cervical metastatic lymph nodes with occult primary; (4) a prospective study in Hong Kong involving the family members of NPC patients to assess the value of EBV serology as a method for early detection of the disease.

165, STUDIES ON EPSTEIN-BARR VIRUS, BURKITT'S LYMPHOMA, NASOPHARYNGEAL CARCINOMA AND INFECTIOUS MONONUCLEOSIS

Klein, G., Karolinska Institutet, Dept. of Tumor Biology, *Solnavagen 1, S10401 Stockholm 60, Sweden*

I. Studies on EBV and other lymphotropic herpesviruses. Changes of transcript patterns following massive induction of the viral cycle by sodium butyrate were studied. The 180K purified EBNA moiety was dissociated into a 53K component, also present in EBV negative B-lymphomas, and a 48K component, carrying the antigenic specificity of EBNA. 53K may be a transformation related component in the B-cell series. HUPNA has a structure similar to that of EBNA. HATNA expression was related to the number of viral (HVA) genomes. At least 16 virus-coded polypeptides were identified by immunoprecipitation. Jijoye cells released transforming virus after butyrate induction. New somatic hybrids were helpful for the understanding of the cellular controls involved in the latency of EBV. EBV receptors were quantitated with purified, radiolabeled virus. Target sizes were estimated for EBV functions by UV inactivation. Clones with high agarose clonability were selected from AT-derived LCL. EBV superconversion changed surface gp-patterns in a BL-like direction. BL lines could be induced to express surface IgD and insulin receptors. Leukemia cell lines could be established from CLL by EBV conversion. EBV receptor bypass experiments were initiated by replacing EBV envelopes with Sendai virus envelopes. The BL-associated 8;14 reciprocal translocation was identified in Burkitt-type leukemia (B cell-ALL). Diploid LCL grew progressively in immunologically privileged sites of nude mice. ADCC titers were correlated with prognosis in both BL and NPC.

II. Cell mediated immunity. EBV specific killer T-cells were isolated from NPC infiltrates and draining lymph nodes. Adherence and killing could be dissociated. Entry of EBV-carrying cells into the lytic cycle increased natural killer (NK) cell sensitivity in a dramatic fashion. Interferon increased the ability of NK cells to kill EBV-carrying LCL. T-cell immunosuppressive conditions are characterized by a peculiar combination of EBV serology and depression of NK and types of other CMI.

166. CONTINUED IMMUNOLOGIC STUDIES ON HUMAN TUMORS

Gunven, P., Karolinska Institutet, Dept. of Tumor Biology, *Solnavagen 1, S10401 Stockholm 60, Sweden*

The objective of the studies is to investigate immune reactions, in particular Epstein-Barr virus-related reactions, in Burkitt's lymphoma and nasopharyngeal carcinoma. Immunofluorescence methods, radioimmunoprecipitation and cytotoxicity tests are used. The findings support the monoclonal B cell nature of Burkitt's lymphoma and indicate the presence of immune complexes with EBV specificity before very late recurrences of the tumor. The nature and significance of such complexes are the subject of continued study.

167. STUDIES ON IMMUNOGENICITY OF MEMBRANE SOLUBLE ANTIGENS EXTRACTED FROM NASOPHARYNGEAL CARCINOMA

Kawamura, A., Tsukuda, M., Sawaki, S., Takada, M., Yosimura, N., Yanoma, S., University of Tokyo, Inst. of Medical Science, Dept. of Immunology, *P.O. Takanawa, Tokyo, Japan*

Nasopharyngeal carcinoma membrane soluble antigens (NPC MS-Ag) have been prepared from NPC-204 cultured cells by hypotonic saline membrane extract procedure (Hollinshead et al.). Qualitative and quantitative studies have been performed on specific immunogencity of these antigens.

From the standpoint of differences in EB virus specific and organ specific antigenicity, MS-Ag of other tumor cells, KB cells (EBNA negative NPC), Raji cells (Burkitt's lymphoma), and PC-1 cells (lung carcinoma) have been studied simultaneously.

In the future, following prospective studies, these NPC MS-Ag could be applied to estimate clinical status and specific immunotherapy of NPC patients.

168. IMMUNOLOGICAL AND MOLECULAR HYBRIDIZATION STUDIES OF NASOPHARYNGEAL CARCINOMA

Ablashi, D. V., Aaronson, S., O'Conor, G., Levine, P., Prasad, U., Bengali, Z., Armstrong, G., Allouache, A., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Laboratory of Cellular & Molecular Biology, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The summary for this project is under entry no. 7.

169. THE SEROEPIDEMIOLOGY OF THE EPSTEIN-BARR VIRUS (EBV)

Henle, W., Klein, G., Olweny, C. L., Nkrumah, F. K., Ziegler, J. L., De The, G., Lanier, A. K., Ho, C. H., Children's Hospital of Philadelphia, Division of Virology, *3400 Civic Ctr. Blvd., Philadelphia, Pennsylvania*, 19104, United States of America

The summary for this project is under entry no. 2.

170. EPSTEIN-BARR VIRUS MARKERS IN NASOPHARYNGEAL TUMORS

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OBJECTIVE: Determine the clinical significance of Epstein-Barr virus immunovirology in the diagnosis and clinical management of American patients with defined histopathological types of nasopharyngeal carcinoma and with metastatic cancer in the head and neck area from an unknown primary.

171. APPLICATION OF EBV MARKERS TO DIAGNOSIS AND PROGNOSIS OF NPC AND OCCULT TUMORS OF NASOPHARYNX AREA IN AMERICANS (ABBREV)

Hyams, V., U.S. Dept. of Defense, Armed Forces Inst. of Pathology, *c/o Walter Reed Medical Ctr., Washington, District of Columbia*, 20306, United States of America

OBJECTIVES: The contractor provides support to the Mayo Foundation NO1-CP9-1006, by supplying clinical information and materials and histopathology consultation.

MAJOR FINDINGS: The contractor has enrolled four nasopharyngeal carcinoma (NPC) patients in the study and has participated in meetings with other collaborative groups for (1) development of data forms for reporting clinical, pathological, therapy, and follow-up information on each patient, and for (2) standardization of descriptive histopathological terminology.

SIGNIFICANCE TO BIOMEDICAL RESEARCH AND THE PROGRAM OF THE INSTITUTE: This project provides support for a contract to demonstrate that Epstein-Barr virus assays can be used for improved diagnosis and management of American patients with head and neck tumors. It is anticipated that the knowledge gained could be transferred to cancer centers for wider application in cancer control. The study will further permit assessment of the specificity of the viral markers in the identification of high risk populations and assessment of other environmental factors contributing to the etiology of nasopharyngeal carcinoma.

PROPOSED COURSE: This project will continue without change.

172. APPLICATION OF EBV MARKERS TO DIAGNOSIS AND PROGNOSIS OF NPC AND OCCULT TUMORS OF NASOPHARYNX AREA IN AMERICANS (ABBREV)

Lanier, A., U.S. Dept. of Health & Human Services, Public Health Service, Health Services Admin., Indian Health Service, *5600 Fishers Ln., Rockville, Maryland*, 20852, United States of America

OBJECTIVES: This contractor will provide support to the Mayo Foundation N01-CP9-1006, by supplying clinical information and materials.

MAJOR FINDINGS: The Indian Health Service has enrolled 17 nasopharyngeal carcinoma patients in the collaborative study.

SIGNIFICANCE TO BIOMEDICAL RESEARCH AND THE PROGRAM OF THE INSTITUTE: This project provides support for a contract to demonstrate that Epstein-Barr virus assays can be used for improved diagnosis and management of American patients with head and neck tumors. It is anticipated that the knowledge gained could be transferred to cancer center for wider application in cancer control. The study will further permit assessment of the specificity of the viral markers in the identification of high risk populations and other environmental factors contributing to the etiology of nasopharyngeal carcinoma.

PROPOSED COURSE: This project will continue without change.

173. HERPES VIRUS ANTIBODIES IN PATIENTS WITH ORAL CANCER

Shillitoe, E. J., University of California, San Francisco Campus, School of Dentistry, Dept. of Oral Medicine & Hospital Dentistry, *551 Parnassus Ave., San Francisco, California*, 94122, United States of America

Oral cancer has been associated with the oral strain of herpes simplex virus, HSV-1, by small-scale studies of cell-mediated immunity. Cancer of the uterine cervix has been closely associated with the genital strain of herpes simplex virus, HSV-2, by studies of antibodies of the virus.

Serum will be collected from patients with oral cancer or leukoplakia attending an Oral Medicine clinic, and will be examined for HSV-1 antibody by measurement of the neutralization constant. An increased activity of HSV-1 antibody will be sought in patients of each group, as compared with controls matched for age, sex and smoking habits. The immunoglobulin class of antibodies to herpes simplex virus will be examined in patients with cancer, leukoplakia, primary herpetic stomatitis or recurrent herpes labialis and in control subjects. The hypothesis that after an acute herpetic infection, only antibody of the IgG class persists, and that appearance of antibody in other immunoglobulin classes is evidence of a recurrent infection, will be tested. If sera from cancer patients contain herpes simplex antibody of non-Ig class, this would be evidence for a continuing stimulus by herpes simplex antigens, from the tumor.

Sequential studies will determine whether an increased antibody neutralization constant in patients with leukoplakia indicates an increased risk of transformation into carcinoma. Patients with oral cancer will be observed repeatedly to find if a high or rising neutralization constant indicates a good prognosis, as has been reported for cervical cancer.

174. CANCER DRUG EFFECTS ON PATIENT SUPPRESSOR CELLS

Harris, J. E., Braun, D. P., Rush University, School of Medicine, Dept. of Internal Medicine, *1725 W. Harrison St., Chicago, Illinois,* 60612, United States of America

We propose to monitor immunologically selected patients with breast cancer, bowel cancer, lung cancer, head and neck cancer, and malignant melanoma who are receiving treatment with combinations of cytotoxic drugs in order to ascertain whether such treatment has in some patients a selective differential suppressive effect on host immunoregulatory suppressor and effector cell mechanisms. With serial assessment points taken before, during and at intervals after chemotherapy, the kinetics of recovery of lymphocyte response to mitogenic stimulation and the effects on the rate and extent of recovery of suppressor cell mechanisms will be measured. An attempt will be made to correlate 'rebound-overshoot' patterns of immune recovery when they occur with an inhibition by chemotherapy of suppressor mechanisms which may persist through the post-treatment interval and to relate these observations to the effect of chemotherapy on numbers of B-cells and T-cells, T-cell subsets (TG and TM cells) and monocytes. The effect of cytotoxic drug treatment on three other parameters of immune function in cancer patients will also be studied. The first of these, the in vitro generation of cytotoxic cells against allogeneic target cells, may reflect afferent host anti-tumor immune capacity. The second, the leukocyte adherence inhibition (LAI) phenomenon is perhaps the most sensitive and specific of those in vitro correlates of cell mediated anti-tumor immune reactivity. The third, an assessment of monocyte activation by quantitation of monocyte chemiluminescence, may reflect host capacity for nonspecific anti-tumor immunity. The influence of patient serum on each of these immune functions will be evaluated. The results of our investigation will provide a clearer appreciation of the immunobiological interactions between cytotoxic chemotherapy and host immune respones in human malignant diseases. The results obtained will provide the basis for improved assessments of patient prognosis and the more rational and effective scheduling of programs of treatment with chemotherapy or chemoimmunotherapy.

175. TRANSFER FACTOR IMMUNOTHERAPY IN CANCER - CLINICAL APPLICATIONS AND BASIC PROPERTIES

Vetto, R. M., Burger, D. R., Vandenbark, A. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Surgical Service, *Sam Jackson Park Rd., Portland, Oregon,* 97207, United States of America

Progress on this project has been achieved in 2 major areas: (1) Fractionation and characterization of transfer factor (TF). (2) Detection of reactivity to tumor antigens in cancer patients by the leukocyte adherence inhibition (LAI) test, and by a new approach, the antigen binding cell assay.

Transfer factor activity measured by the transference of delayed type skin test reactivity from immunized donors (humans or calves) has been characterized by chemical separation (high pressure liquid chromatography and isoelectric focusing) and enzymatic treatment (alkaline phosphatase, pronase, proteinase K, and phosphodiesterase I and II). Results suggest TF separates as a dislinite entity of low molecular weight and strongly negative charge and has both peptide(s) and nucleotides as structural components. Melanoma neuroblastomic and leukocyte adherence inhibition test used to evaluate immunifying patients with squamous cell carcinoma of the head and neck and families with a high incidence of melanoma has detected higher levels of reactivity within specific tumor groups to their appropriate tumor extract. The mechanism involved in this assay includes reactions by multiple cell types, and serum factors from immune donors which can arm nonimmune cells to be reactive to specific tumor extracts. The antigen binding cell assay - which measures formation of rosettes between immune cells and tumor antigen-conjugated red cells - has detected an increased percentage of mononuclear cells which can bind squamous carcinoma antigen in patients with advanced primary tumor but not in patients with recurrence or in controls.

176. USE OF CELL KINETICS TO PLAN HUMAN TUMOR TREATMENT

Barranco, S. C., University of Texas, Medical Branch at Galveston, School of Medicine, Dept. of Human Biological Chemistry & Genetics, *300 University Blvd., Galveston, Texas,* 77550, United States of America

The overall objectives of this proposal are to design and test optimal strategies of cancer treatment in humans based on the concepts of the cell cycle and tumor cell population kinetics (Project A). Human tumors such as melanomas, carcinoma of the cervix, and epidermoid carcinoma of the head and neck are accessible for multiple biopsies and for growth kinetics studies such as cell cycle times and growth fractions. Our preliminary studies show that sequential and systematic kinetics analyses of biopsy specimens before, during, and after treatment with a single drug or radiation allow more accurate scheduling of subsequent agents and have led to improvements in response rates. Several intermediate research objectives will be concerned with the development of mathematical models and computational techniques to characterize human tumor growth and to predict and evaluate response to kinetics-based therapy (Project B). By using human tumor kinetics data obtained by FMF analysis in conjunction with appropriate mathematical models and computational techniques (which have been developed and described in Project B), one can readily determine the in vivo kinetics effects of drugs and radiation. Some treatment protocols developed from such modeling studies may depart radically from accepted standard treatment modalities and these will be tested in the 15091A anaplastic carcinoma model in A/J strain white mice (Project C). In addition, this animal model will be used to further characterize and explore the kinetics effects of drugs, radiation and hyperthermia combinations, and fractionations.

Our overall goals, therefore, are to expand our kinetics studies in human tumors; to obtain more accurate data on recruitment and synchrony; and to develop kinetics-based mathematical models which will be used for the design of more effective treatment protocols.

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177. CELLULAR KINETICS OF CLINICAL CANCER CHEMOTHERAPY

Straus, M. J., Wotiz, H. H., Del Guercio, L. R., Madden, R. E., Rohman, M., Addonizio, J., Smith, F. B., Thelmo, W., Glasser, M., New York Medical College, Westchester Campus, School of Medicine, Dept. of Medicine, *Valhalla, New York,* 10595, United States of America

In this program project, we have outlined a series of studies which may have potential use in the design of more optimal therapeutic approaches in human solid tumors. In the cell kinetics projects, we have proposed to analyze the perturbation effects of various drugs on cell cycle in human lung, breast and head and neck cancers. We will correlate cytokinetic parameters with prognosis and response to therapy. We will compare simultaneously derived cell cycle parameters and estrogen and progesterone receptor proteins in breast cancer tissue. In animal kinetic studies, we will attempt to develop a comprehensive model to describe cytosine arabinoside and hydroxyurea by analyzing cell cycle perturbation effects with pulse and continuous infusion administration in tumor cells, bone marrow and ileum. These studies will be done in concert with biochemical pharmacologic analyses to determine the relationship of drug metabolites and perturbation. In a new tumor model, the MXT hormone dependent mouse mammary carcinoma, the relationship of cytokinetics and hormone receptors will be analyzed. The clinical program includes studies for lung cancer, prostate cancer and Phase II protocols for various solid tumors designed on the basis of cytokinetic concepts. These studies attempt to improve therapeutic results and serve as a basis to test perturbation effects of the modalities on cell populations.

178. SCREENING RELATIVES OF PATIENTS WITH MEDULLARY CARCINOMA

Wells, S. A., Duke University, School of Medicine, Dept. of Surgery, *Box 3711, Durham, North Carolina*, 27710, United States of America

OBJECTIVES: Perform periodic screening of relatives of patients with medullary carcinoma of the thyroid using calcitonin radioimmunoassay. Provide accurate, sensitive, and specific measurements of immunoreactive calcitonin on samples of plasma or tissue from patients suspected of having medullary carcinoma of the thyroid. Radioimmunoassays will be performed as needed to screen subjects for the presence of disease, or to follow the clinical progress of disease treated by surgery or chemotherapy. The primary responsibility will be the measurement of samples obtained from patients followed in our MEN-II kindreds. Assay samples sent by other physicians in the southeastern United States if these physicians can provide basic clinical information on each patient. The information thus obtained may result in the discovery of new cases which might enter the study.

179. FAMILIAL INCIDENCE AND MULTIPLE MANIFESTATIONS OF MEDULLARY CARCINOMA OF THE THYROID

Williams, G. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Nuclear Medicine & Endocrinology Section, *820 S. Damen Ave., Chicago, Illinois*, 60612, United States of America

The purpose of this study continues to be to evaluate all family members of patients with diagnosed medullary carcinoma of the thyroid. This evaluation includes a) clinical evaluation, b) serum calcitonin by radioimmunoassay before and after calcium infusion, c) serum parathyroid hormone by radioimmunoassay, d) determination of urinary catecholamines. In any patients in whom abnormalities are found, appropriate therapy will be carried out. In those subjects in whom the studies are normal, repeat studies will be done at 6 to 12 month intervals. In this way, this study should a) lead to early diagnosis and treatment of patients with medullary carcinoma of the thyroid before clinical manifestations are apparent, and b) yield additional information about the incidence, inheritance and natural history of this disease.

During the past year, 5 additional new patients suspected of medullary carcinoma of the thyroid have been evaluated, but the studies were normal in all of these patients. The one patient who was identified as a strong suspect for medullary carcinoma of the thyroid three years ago has been in Europe and is still unavailable for reevaluation. This patient will be more thoroughly investigated and her family members will be evaluated as soon as she returns to this area.

180. SALIVARY GLANDS, POLYAMINES AND CHEMOTHERAPY

Brown, D. G., Ghoneim, S., Southern Illinois University, Edwardsville Campus, School of Dental Medicine, Dept. of Biomedical Sciences, *Edwardsville, Illinois*, 62025, United States of America

The summary for this project is under entry no. 131.

181. AN ANALYSIS OF INTRATUMOR CHEMOTHERAPEUTIC DRUG LEVELS

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OBJECTIVE: To determine the intratumor levels of chemotherapeutic agents in patients with head and neck cancer.

PLAN: Tumors are biopsied at specified intervals following chemotherapy. Simultaneous blood levels of drug are also determined and compared to intratumor levels of drug.

METHODOLOGY: Tumor and blood drug levels of cis-platinum, bleomycin and methotrexate are measured using high performance liquid chromatography and RIA techniques.

FINDINGS: To date, three patients have had their tumors biopsied after receiving the chemotherapeutic agents cis-platinum, bleomycin, and methotrexate. To date none of the tumor specimens or blood specimens have been analyzed for drug levels. All specimens are frozen in liquid nitrogen so that all tumor specimens and blood specimens may be run simultaneously. We anticipate that this will take place in about four months when we have accrued six patients on the study.

182. RADIATION-INDUCED THYROID CANCER

Schneider, A. B., Frohman, L., Pinsky, S., University of Chicago, Michael Reese Hospital & Medical Center, Dept. of Medicine, *2929 S. Ellis Ave., Chicago, Illinois*, 60616, United States of America

The summary for this project is under entry no. 21.

183. HYPOTHALMIC-PITUITARY FUNCTION AFTER HEAD AND NECK IRRADIATION (CHILDREN)

Kaplan, S., University of California, San Francisco Campus, School of Medicine, Dept. of Medicine, *551 Parnassus Ave., San Francisco, California*, 94122, United States of America

This is part of a broader project. A summary of this subproject is not available.

C. RADIOGRAPHIC SCANNING AND IMAGING

184. DIGITAL COMPUTER IN SCINTIGRAPHY OF TUMORS

Erjavec, M., Snajder, J., Soklic, M., Kmet, A., Inst. of Oncology, Dept. of Nuclear Medicine, *Zaloska 2, P.P. 17, 61105 Ljubljana, Yugoslavia*

OBJECTIVE: The aim of the study is to improve the results of tumor scanning by use of a digital computer.

APPROACH: Structures within static images are automatically separated, quantitated, and their content expressed in various modes: (I) A known fraction of the administered dose (standard) can be included into the scanning field and results presented either as (1) percentage of the dose within a structure or as (2) a quantitative image where the symbols designate concentration in percentage of doses/cm2 of the image. (II) Alternatively, the 'body background' can be determined and a similar quantitative image produced in terms of target/nontarget ratios.

PROGRESS: These techniques proved to be useful in quantitating 67-Ga uptake in thyroid tumors and are currenty used for in vivo cell cycle studies in 'synchronized' oropharyngeal carcinomas with 99m-Tc bleomycin. Tumor uptake of radiopharmaceuticals can be quantitated and followed after therapy (131-I, 67-Ga). The detection power of tumor-seeking agents can be compared (18-F/85-Sr). Subtraction of dual tracer records can be performed better by computer than by analogue circuitry.

185. THE USE OF COMPUTED TOMOGRAPHY FOR SCREENING OF JAW LYMPHOMA

Kummoona, R. K., Ismail, M., University of Baghdad, School of Dentistry, Dept. of Oral Surgery, *Baghdad, Iraq*

OBJECTIVE: Study of the jaw lymphoma, Middle East variety, a clinical-pathological entity which differs from Burkitt's lymphoma in clinical behavior, response to treatment and possibly in its etiology. The tumor first appears in the premolar-molar region. Children suffering from jaw lymphoma die because of visceral metastasis. The use of postmortem studies in Iraq is severely restricted because of religious reasons and it is difficult to asses which organ was invaded by metastases.

CT scans might asses the extent and distribution of the tumor masses in the visceral organs by metastases, by using both coronal and transverse planes. CT scans were sufficiently characteristic to permit clinical diagnosis of most jaw lymphoma cases with visceral metastasis. Research is in progress to correlate these findings with the causative agent of jaw lymphoma.

186. VALUE OF SIALOGRAPHY AND SCINTIGRAPHY IN DIAGNOSED SALIVARY GLAND DISORDERS

Cagan, M. I., Gill, S. P., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Dental Service, *Martinsburg, West Virginia*, 25401, United States of America

PROJECT OBJECTIVE: The objective of this study was to compare the diagnostic values of sialographic and scintigraphic tests.

PLAN: Eight tests were conducted to determine changes in salivary gland function and structure in patients with salivary gland disorders.

METHOD: A simple sialographic technique using a catheter fitted over a lacrimal probe was performed. For optimal pantomographic study of the salivary glands, a slightly oblique view with the head turned to the side was demonstrated to be of value. Sialograms were evaluated for filling and secretory phases and major ducts were also studied morphologically.

FINDINGS: Examination of the salivary glands by sialography revealed the detailed morphology of the duct system. Clearing radiographs indicated that glands with impaired function had prolonged clearing times. The contrast sialogram was most useful in evaluating recurrent inflammatory disorders, and the radiosialogram found its greatest value in evaluating patients with suspected neoplasms. These examinations should not be used in lieu of a histologic diagnosis in tumor cases except when a smooth margined radiopositive lesion corresponding with a clinically evident Warthin's tumor is noted. Perhaps the most important feature of salivary scintigraphy is its sensitivity in depecting changes in glandular dysfunction.

CLINICAL RELATIONSHIP: From this clinical project it was validated that contrast sialography and radionuclide scanning were complementary procedures used in the evaluation of the salivary glands.

187. TUMOR IMAGING

Larson, S. M., Dobie, R., Cummings, C., Rasey, J. S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *4435 Beacon Ave. S., Seattle, Washington*, 98108, United States of America

The overall objective of the project is to develop new and improved ways for diagnostic imaging of tumors. The project is organized into two parts, the first part related to enhancement of target-to-nontarget ratios of standard single photon emitting radiopharmaceuticals. The second part is related to feasibility of positron emission tomography in imaging of tumors. The methodology we have employed is initially to utilize animal tumor model systems and radioactive tumor seeking drugs to define the biodistribution kinetics and uptake parameters in order to develop ways to improve concentration in tumors relative to other tissues. With respect to positron emission tomography feasibility studies, we have used long-lived analogs of the appropriate positron pharmaceutical in biodistribution studies in animals. For example, we have studied tritiated thymidine uptake into both rodent tumors and spontaneous lymphomas in dogs. Our findings include a new technique for enhancing the uptake of gallium in tumors relative to surrounding tissues, using deferoxamine, an iron chelating agent which also chelates gallium. We have achieved enhancements of 10- to 20-fold over simple equilibration methods. In addition, we have also explored other imaging agents, all in clinical imaging. For example, we have begun to image cobalt-57 bleomycin in head and neck tumor patients. This part of the project is done in collaboration with the Otolaryngology Unit. We have shown that there is very avid accumulation of substrates which could be labelled with positron emitters into tumors in both dog and rodent tumors. In summary, this is a diverse program and some of our methods that have been applied in animal tumors are nearing clinical applicability.

188. USE OF RADIOACTIVE PHOSPHORUS IN EARLY DIAGNOSIS OF RECURRENT CARCINOMA OF THE HEAD AND NECK

Goode, R. L., Goodwin, D., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Surgery Service, *3801 Junipero Serra Blvd., Palo Alto, California*, 94304, United States of America

This project continues and we now use bleomycin-EDTA (BLEDTA) tagged with indium III. We have studied 60 head and neck squamous cell cancer patients to date who have had BLEDTA injections. The tumors ranged in size from 0.6 cm to 8 cm. We have found an 85 percent positive scan rate - the false negatives being seen with the smaller tumors. Positive scans have also been seen in thyroid adenocarcinoma and pulmonary tuberculosis.

D. OTHER DIAGNOSTIC AND PROGNOSTIC FACTORS

189. AN INTERVENTION STUDY OF ORAL CANCER AND PRECANCEROUS LESIONS IN RELATION TO TOBACCO USE IN RURAL INDIAN POPULATIONS

Mehta, F. S., Pindborg, J. J., Hamner, J. E., Daftary, D. K., Gupta, P. C., Aghi, M. B., Tata Inst. of Fundamental Research, Basic Dental Research Unit, *Homi Bhabha Rd., Bombay 400005, Maharashtra, India*

Through follow-up studies for the last ten years it has been established that tobacco usage in the various forms practiced in different parts of India is definitely associated with oral cancer and precancerous lesions. The incidence of precancerous lesions among those who do not practice tobacco habits of any kind was almost zero, whereas incidence among those with such habits ranged from 1 to 35 per 1,000 per year, depending upon the habit. The next step is to find out whether the association between oral cancer and precancerous lesions and tobacco habits is direct by demonstrating a reduction in the incidence of precancerous lesions when the tobacco habits are discontinued. A sample of 12,000 individuals with tobacco habits has been examined and interviewed in each of the three rural areas under study. In order to persuade these villagers to give up their tobacco habits, they are being exposed to a concentrated program of education, motivation and guidance. The villagers are being shown a documentary film, especially made for this purpose, in the vicinity of their homes, in the most suitable format formulated after conducting impact studies of the film in each of the three areas. The message is also communicated personally to each of the examined individuals by trained social scientists. In addition, the population is being subjected to visual, audio and other media support in the form of newspaper articles, posters and radio broadcasts. These individuals are being reexamined annually to assess changes in tobacco habits, development of new oral precancerous lesions and changes in previously diagnosed lesions. The first annual reexamination is complete and the second one in progress.

190. CANCER EDUCATION AND SCREENING PROGRAM FOR TEXTILE AND FURNITURE INDUSTURIES

Heyden, S., Duke University, School of Medicine, Dept. of Community & Family Medicine, *Box 3711, Durham, North Carolina*, 27710, United States of America

The first project, the Cannon Mills Cancer Education and Screening Program in Kannapolis and Concord, North Carolina, was completed in 1977, while other industries are presently participating in similar programs. One of the objectives is to detect specific industrial cancer risks in the textile and furniture industries (e.g., bladder cancer, lung cancer, nose cancer). So far, none of these cancers have shown any appreciable accumulation, i.e., the risk of developing these cancer types appears no higher in the two industries compared to the general population of North Carolina. A description of the first completed project follows: A cancer education and screening program was conducted among 19,000 Cannon Mills workers in North Carolina. Lectures were presented on company time for all employees within each of the three 8-hour shifts. This group education contained information on six cancer types felt to be amenable to screening and in which early detection can be expected to increase survival: breast, cervix, colon, bladder, prostate and oral cavity. After the completion of lectures employees were offered a screening examination. Thirteen thousand employees accepted and were screened between 2/1/76 and 1/31/78. The cost of screening was ten dollars per person.

Thirty-two asymptomatic patients who participated in the screening were discovered to have cancer. The compliance among those who had positive findings, and who were advised to see their M.D.'s was 90% among female and 81% among male employees.

The program received unanimous approval of the Carbarrus County Medical Society, which has recommended it for other counties. The state of North Carolina has also adopted this program as a pilot program among 10,000 state employees, with the assistance of Blue Cross/Blue Shield.

191. A PILOT DEMONSTRATION DETECTION PROGRAM

Greco, V. F., Schulman, N., Tucker, R. S., Teitelbaum, C., Community Cancer Corp. of Luzerne County, *Box 1343, Wilkes Barre, Pennsylvania,* 18703, United States of America

This pilot detection program is the first effort in implementing a cancer control plan, begun by area physicians several years ago and supported in part by a Cancer Center Planning Grant. The pilot proposes to use specially trained nurse clinicians to perform screening tests and examinations in Luzerne County, Pennsylvania. During the three-year program, nurses, recruited from the community and trained at Hahnemann Oncologic Institute, will perform complete screening examinations in two hospital-based clinics. A projected population of 10,944 people over the age of 40 will be screened for cancer of the mouth, throat, cervix, prostate, breast, skin, and rectum.

Demonstration pilot efforts include the training and utilization of nurse clinicians in this unique fashion, study of variables in patient participation, acceptance of nurse clinicians by both patients and physicians, examination of the validity and reliability of this form of community based cancer screening, analysis of cost variables and the progressive development of programmatic self-support by the community. The pilot is further designed to encourage the introduction of a single county tumor registry and to encourage additional epidemiologic research in future years although funds are not requested for these purposes here.

The applicant is the Community Cancer Corporation of Luzerne County (CCC), a new non-profit corporation which has been created to plan and manage this and other cancer related service projects. The corporation and indeed this pilot request are an outgrowth of the extremely high incidence of cancer in the county, the high degree of physician and community support for the project and the potential applicability of the pilot to other similar regions of the country.

192. ELECTRON MICROSCOPIC STUDIES ON MATERIAL OBTAINED BY FINE NEEDLE BIOPSY

Engstrom, H., Engstrom, B., Hagelqvist, E., University Hospital, Dept. of Otolaryngology & Clinical Cytology, *S75014 Uppsala 14, Sweden*

The objective of this research is to improve methods for examination of material acquired by fine needle biopsy aspirations. Electron microscopic techniques applied to such material enable reproducible and fast observation of tumor cells and characterization of many structural details of diagnostic importance which cannot be obtained with light microscopy.

Special methods have been developed for the handling of the specimens and the materials can if necessary be ready for electron microscopy investigations within 6 hours.

The study began in 1972 and it now includes about 350 cases of tumors especially from the head and neck region. Many of them are salivary gland tumors. Originally the material was chiefly used for methodological studies, but it has become more evident that the specimens provide important diagnostic clues.

It is not yet possible to fully define the diagnostic value of the method, although it has already contributed significantly to our understanding of the cytology of light microscopic specimens and the internal structure of tumor cells.

The method appears to be quite helpful in preoperative diagnostics in cases where light microscopic examinations do not provide sufficient information, especially in cases where open biopsy is not desirable, e.g., in salivary gland tumors. Since fine needle aspirations can be repeated several times with little risk or discomfort for the patient, TEM studies can be used to follow and evaluate the results of a treatment using irradiation or cytotoxic drugs. The results are promising.

193. EFFECT OF TUMORS ON EUSTACHIAN TUBE AND HEARING

Myers, E. N., Beery, O. C., Bluestone, C. D., Bjuro Moller, M., Sigler, R. N., University of Pittsburgh, Eye & Ear Hospital of Pittsburgh, Dept. of Otolaryngology, *230 Lothrop St., Pittsburgh, Pennsylvania,* 15213, United States of America

Otitis media with effusion is frequently seen in patients with tumors of the head and neck. The presence of effusion may be related to functional or mechanical blockage of the Eustachian tube. Dysfunction of the Eustachian tube-middle ear system may result in hearing loss or medical complications. The purpose of this investigation is to evaluate Eustachian tube-middle ear function in patients with head and neck tumors pre- and post-treatment. Treatment groups include surgery, radiation, combined surgery and radiation, and combined surgery, radiation and adjuvant chemotherapy. Methods of assessment include otoscopy, audiometry, tympanometry, acoustic reflex, and Eustachian tube ventilatory function testing. From this study information on the incidence of Eustachian tube-middle ear problems and hearing loss and the effect of type of treatment on Eustachian tube-middle ear function and hearing acuity will be obtained. Knowledge of this problem will aid in diagnosis and treatment so that the quality of life of patients with head and neck tumors can be maximized.

194. STUDY OF WOODWORKERS IN FURNITURE INDUSTRY - A HIGH RISK GROUP FOR ADENOCARCINOMA OF SINUSES

Hadfield, E. H., Macbeth, R. G., Wycombe General Hospital, *High Wycombe, England, United Kingdom*

The high risk group of woodworkers in furniture industry is examined annually (at the workers' work place) by R.G. Macbeth. When some clinical change is visible in their noses they are sent to E.H. Hadfield at the hospital for biopsy and/or treatment.

195. COMPLICATIONS CAUSED BY RADIATION THERAPY IN THE ORAL CAVITY AND THEIR PREVENTION

Nurotio, U. K., Kuopion Korkeakoulu, *P.O. Box 138, SF70101 Kuopio 10, Finland*

OBJECTIVES: To determine complications in the oral cavity resulting from radiation therapy of head and neck tumors in a northeastern Finland population. To find new methods of prevention to protect teeth, salivary glands and other tissues in the oral cavity from unwanted irradiation.

196. SYMPTOMATOLOGY AND RISK FACTORS OF CANCERS OF THE LARYNX AND OF THE HYPOPHARYNX

Raymond, L. M., Lehmann, W., Tuyns, A., Registre Genevois des Tumeurs, Centre de cytologie et de depistage du cancer, *55 Blv. de la Cluse, 1205 Geneva, Switzerland*

The summary for this project is under entry no. 45.

197. EARLY DIAGNOSIS OF MEDULLARY CARCINOMA OF THE THYROID IN MULTIPLE NEOPLASIA (HUMAN)

Wells, S. A., Duke University, School of Medicine, Dept. of Surgery, *Box 3711, Durham, North Carolina,* 27710, United States of America

This is part of a broader project. A summary of this subproject is not available.

198. RADIATION-ASSOCIATED THYROID CARCINOMA

Shimaoka, K., Wallace, H. J., Roswell Park Memorial Inst., Dept. of Medicine, *666 Elm St., Buffalo, New York,* 14263, United States of America

A program has been instituted to screen annually by clinical and laboratory examinations those persons who have received radiation therapy to the head and neck areas for benign conditions. Those found to have goitre are further evaluated and treated by suppressive therapy with thyroid hormone. Those who respond are continued on long-term drug therapy, while those whose goitres increase in size are offered thyroidectomy. The natural history of radiation-associated benign and malignant thyroid diseases is being studied.

199. PREVENTION, DETECTION AND CONTROL OF RADIATION ASSOCIATED THYROID CANCER

DeGroot, L. J., University of Chicago, Pritzker School of Medicine, Dept. of Medicine, *5801 S. Ellis Ave., Chicago, Illinois* 60637, United States of America.

This is part of a broader project. A summary of this subproject is not available.

200. NASOPHARYNGEAL CANCER - DIAGNOSTIC/PROGNOSTIC TESTING

Glaser, R., Ohio State University, Columbus Campus, School of Medicine, Dept. of Medical Microbiology & Immunology, *370 W. 9th Ave., Columbus, Ohio,* 43212, United States of America.

No summary has been provided to the Smithsonian Science Information Exchange.

V. CLINICAL THERAPY

A. RADIOTHERAPY

201. BIOLOGIC EFFECT OF FRACTIONATED RADIOTHERAPY FOR LARYNGEAL CANCER

Hansen, H. S., Hjelm Hansen, M., Sorensen, P. B., Finseninstitutet, Radium Centre, *Strandboulevarden 49, DK2100 Copenhagen, Denmark*

OBJECTIVE: The aim is to identify the dose-response curves valid for fractionated radiotherapy in treatment of laryngeal carcinoma. Dose may be the physical absorbed dose or any measure of the biologic effect of the given treatment, estimated by use of mathematical models combining the effect of absorbed dose, fractions, time, tumor size and field size. Dose-response curves for tumors as well as for normal tissues will be determined.

APPROACH: The radiotherapy schedule that is utilized will be recorded in detail in a computer and all existing fractionation models will be used in order to obtain estimates of the biological effective dose.

Clinical findings - especially such as residual tumor/local recurrence, lymph node metastases, death and complications after irradiation and/or secondary surgery - will be recorded and the frequency of these events calculated as functions of the different measures of biologic dose in order to construct the dose-response curves.

PROGRESS: It is already known from the literature and from similar studies in Denmark that dose-response curves do in fact exist. It is also known from a pilot study that dose-response is to be expected in the present material. By combining the data it is hoped that dose-response curves may be found with sufficient accuracy to allow an optimization of the treatment.

202. RADIOTHERAPEUTIC CONTROL - MULTIPLE DAILY TREATMENT SESSIONS

Cappellini, M., Cellai, E., Chiavacci, A., Olmi, P., Pirtoli, L., Mungai, R., Fallai, C., Universita degli Studi di Firenze, Istituto Interfacolta di Radiologia, Policlinico Universitario, *Viale Morgagni, 50144 Florence, Italy*

The aim of the protocol is to assess the value of multiple daily fractionations (MDF) of the dose in the treatment of head and neck cancers; results of this treatment are compared with those obtained with conventional daily treatment.

The tolerance with both fractionation schedules is of the same order. Between July 1980 and December 1980 18 other patients were treated with MDF and to date 83 patients have been included in the protocol. These cases are distributed as follows: 33 oral cancers; 39 oropharyngeal cancers; 11 maxillary antrum cancers.

The preliminary results are encouraging and the study continues. A larger number of cases must be collected to achieve more definite results.

203. RELATION BETWEEN PROLIFERATIVE ACTIVITY AND CLINICAL RESPONSE OF ORAL CARCINOMAS TO RADIOTHERAPY

Molinari, R., Silvestrini, R., Chiesa, F., Costa, A., Costa, L., Istituto Nazionale per lo Studio e la Cura dei Tumori, Dept. of Clinical Oncology C, *1 Via G Venezian, 20133 Milan, Italy*

OBJECTIVE: To study the correlation between kinetic and clinicopathological characteristics of primary tumors. To rationalize the choice and sequence of different clinical treatments on the basis of the proliferative changes induced by radiotherapy.

APPROACH: The study is carried out on untreated patients. Tumor biopsy specimens are cut into small fragments and incubated for 1 hour at 37 degrees C with 3H-thymidine. Autoradiographs of histological sections are performed with stripping film techniques. The kinetic determination is carried out before and after 10 Gy (2 Gy/day for 5 days, using 60Co unit).

PROGRESS: The determination of proliferative activity carried out on 27 patients before and after the treatment with 10 Gy showed that the pretreatment LI value is not indicative of the variation induced by radiotherapy. The variation of proliferative activity observed after treatment with 10 Gy is not indicative of early clinical response (tumor volume reduction), while it is significantly indicative of disease-free survival (p less than 0.005).

204. TREATMENT OF LOCALIZED ADVANCED HEAD AND NECK CANCER WITH HIGH DOSES OF INTERMITTENT RADIATION

Gaitan, A., Gonzalez, R., Instituto Nacional de Cancerologia, Seccion de Radioterapia, *Apartado Aereo #17.158, Calle 1 No. 9-85, Bogota, DE, Colombia*

OBJECTIVE: To determine the effectiveness of high intermittent doses of radiation in the treatment of localized, advanced cancer of the head and neck.

MATERIAL: Patients with localized advanced head and neck cancer (T3, T4, and/or N3)

METHOD: Supervoltage radiation, 2,400 rads in 3 weeks (3 fractions). (Translated)

205. EXCLUSIVE RADIOTHERAPY WITH CO60 AND CS137 IN CANCER OF THE FLOOR OF THE MOUTH

Bravo Soto, S., Llanos Cifuentes, E., Hospital Regional de Concepcion, Servicio de Radioterapia, *Janequeo 200, Concepcion, Chile*

OBJECTIVE: To determine rates of loco-regional control, complications and survival.

APPROACH: External telecobalt therapy, 5,000 rads over five weeks, to the primary lesion and neck, followed by Cs137 needles overlaid on the primary lesion only. Calculations are performed according to the rules of Paterson and Parker with M.D. Anderson Hospital system for correction of radiographic calculations. In patients with clinical disease of the neck, selective dissection of the tumoral mass that was first palpated six weeks after terminating external therapy. In patients with loco-regional failure, surgical rescue is employed.

206. RTOG 79-13 - PROTOCOL TO STUDY TWO RT FRACTIONS PER DAY IN TREATMENT OF SQUAMOUS CELL CANCER OF ORAL CAVITY, PHARYNX, LARYNX AND SINUSES

Bogardus, C. R., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Radiology Service, *921 N.E. 13th St., Oklahoma City, Oklahoma,* 73104, United States of America

OBJECTIVES: 1) To determine if local control of primary head and neck cancer can be improved using hyperfractionation over conventional fractionation. 2) To evaluate patient acceptance and tolerance of normal tissue to twice daily fractionated treatment. 3) To determine if inoperable lesions can be made operable by altered fractionated technique of administering radiation therapy. 4) To determine survival rates of each fractionated technique.

RESEARCH PLAN: Patients will be randomized according to site and stage of tumor. Arm A: Conventional RT, 600 rad in 33 fractions to 7380 in 41 fractions at 180-200 rad per fraction, 5 fractions/week. Arm B: Two fractions per day of 120 rad separated by 3-6 hours, 6000 rad, 5 weeks.

Criteria of response (CR, PR, MR, NC, PD) will be made at day 90 to 120; weekly measurements will be made of the status of the neck, during the course of therapy. In addition assessments will be made of the degree of rehabilitation of the patient, swallowing function, and performance status.

STATISTICAL CONSIDERATIONS: 1) For a majority of the patients in both arms, high dose photon therapy will be the only treatment. 2) For the various disease sites the 2-year survival can vary from 10-15% to 40-50%. 3) With 4-5 institutions participating in this study the accession rates should be 50 cases per year from all the disease sites. 4) In order to show a statistically significant 11-15% difference in the local controls, over 100 patients from each site will be required. Therefore, it should take from 2-3 years to complete this investigation.

207. FAST NEUTRON BEAM RADIOTHERAPY

Griffin, T. W., Groudine, M. T., Laramore, G. E., Russell, A. H., Tong, D., Wootton, P., Eenmaa, J., University of Washington, School of Medicine, Dept. of Radiology, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington*, 98195, United States of America

The objective of this study is to determine whether fast neutron teletherapy has any advantage over conventional photon teletherapy in the treatment of cancers in humans. The basis for a potential advantage is that hypoxic tumor cells respond better to high LET radiation than conventional photon radiation. Therefore, in those cancers containing even small (1%) components of hypoxic cells, a potential cause of tumor persistence after conventional photon radiation therapy can be reduced or eliminated.

The objective of the physics component is to deliver a controlled quantitated beam of fast neutrons coupled with methods of patient handling alignment and treatment planning such that a valid evaluation of fast neutrons as a treatment modality may be expedited.

The radiation oncology goals are to study tissue tolerance and tumor response to patterns of treatment and initiate cooperative trials with other fast neutron beam therapy centers.

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208. PROTON RADIATION THERAPY RESEARCH

Suit, H. D., Goitein, M., Verhey, L., Koehler, A. M., Schneider, R., Linggood, R. M., Wang, C. C., Shipley, W. U., Gunderson, L., Choi, N. C., Epp, E., Massachusetts General Hospital, Dept. of Radiation Medicine, *32 Fruit St., Boston, Massachusetts*, 02114, United States of America

An exploratory study of fractionated large field proton therapy is proposed. We describe work already performed in the investigation of proton irradiation. This includes investigation of the problems posed by heterogeneity and a description of patients treated by us at the Harvard Cyclotron Laboratory.

The objectives of the study are: (1) to evaluate the potential clinical advantages of proton therapy for selected tumor-normal tissue situations through critical evaluation of comparative treatment plans and treatment of selected patients; (2) to assess the problems posed by tissue heterogeneity through theoretical calculations, use of a CT scanner in a variety of anatomic sites, and confirmatory measurements in proton beams; (3) to make improvements to the treatment facility which will permit routine treatment of a substantial number of patients with one fraction per day and with reliability of dose delivery and beam quality; (4) to measure the proton RBE for small fractionated doses with number of end points; (5) to treat a number of patients with protons in situations in which protons appear to offer an advantage and for which the heterogeneity problem is surmountable; (6) to plan a prospective clinical trial of proton vs. photon therapy; and (7) to design these clinical trials, to the extent feasible, to provide control information for work with pi-meson or heavy ion therapy.

If this program continues to demonstrate significant advantages for the highly localized dose distributions that can be achieved with proton beams, it will offer the potential for improved local control and/or reduction of morbidity for a large class of cancer patients.

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209. MICROWAVE DIATHERMY AND RADIOTHERAPY OF MALIGNANT TUMORS

Worde, B. T., U, R., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *508 Fulton St., Durham, North Carolina*, 27705, United States of America

Boyd T. Worde, M.D., has taken over this project which was previously directed by Lowell S. Miller, M.D. (project number 239-14-1554-5730-01). This ongoing clinical study using microwave-induced hyperthermia immediately following conventional photon radiotherapy is to evaluate the response of normal tissues, the regression of cutaneous or subcutaneous tumors, and the practical feasibility of such combined modalities in therapeutic radiology. Ionizing radiation in individual fractions of 200-600 rad has been used 2-5 times/week to total doses of 1400-6000 rad in 5-30 fractions. Each microwave (42.0-43.5 degrees C) session was of 45 minutes duration, administered 2-3 times/week, with a maximum of 14 sessions in 5 weeks. The 30 patients treated to date have had squamous cell ca., breast ca., malignant melanoma, epithelioid sarcoma, undifferentiated ca., and liposarcoma involving most body surface areas, including head and neck region. Most of the patients treated had far advanced malignancies relentlessly progressing despite previous surgery, radiation, chemotherapy, and immunotherapy. Despite this, microwave hyperthermia in combination with radiotherapy offers the possibility of substantial impact on clinical cancer therapy, whether of curative or palliative intent. We have found that 1) local hyperthermia with microwave alone or in combination with ionizing radiation can be used with excellent normal tissue tolerance, providing that local tissue temperatures are carefully monitored and controlled; 2) a significantly higher level of preferential heat induction into tumor tissue as compared to surrounding normal tissues; 3) repeated microwave hyperthermia at 42.0-43.5 degrees C for 45 minutes per session immediately following photon irradiation yields a favorable therapeutic ratio, often with dramatic results.

B. CHEMOTHERAPY

210. COMPARISON BETWEEN BASAL CHEMOTHERAPY GIVEN BY INTRA-ARTERIAL INFUSION AND A SIMILAR REGIMEN GIVEN SYSTEMICALLY (ABBREV)

Stephens, F. O., Harker, G. J., Sydney Hospital, Surgical Oncology Unit, *Macquarie St., Sydney, N.S.W. 2000, Australia*

The aim is to compare the value of chemotherapeutic agents given as basal treatment by intra-arterial infusion prior to radiotherapy and/or surgery with the value of a similar regimen of agents given by intravenous or other systemic administration. The objective will be to assess the immediate degree and rate of desired response to these agents, and also to compare the incidence, degree and range of side effects, as well as the comparative expense and simplicity of the two methods of administration. Ultimately, recurrence free periods and survival times will be compared. Historical controls will also be evaluated.

Squamous cell carcinoma of the head and neck is the tumor primarily under investigation. Patients who have not had previous attempts at definitive therapy are included; thus the neoplasm is contained in otherwise normal healthy tissue with normal blood supply unaltered by previous surgery or radiotherapy. Lesions are also of such magnitude, or of such a type, that cure by traditional means would be unlikely. Control intravenous patients are patients who, for physical, psychological, social or other reasons, are considered unsuitable for intra-arterial infusion requiring a month or so of confinement in hospital.

Chemotherapeutic agents include hydroxyurea, bleomycin, vincristine, actinomycin D, and methotrexate. Each drug is given in 1 liter of fluid infused over 24 hours; 10,000 units of heparin are added to each liter. The cycle lasts for five days followed by two rest days using heparinized saline only. Most patients then receive follow-up radiotherapy and/or surgery; even when regression is apparently complete, microscopic disease is always considered a possibility.

211. EVALUATION OF INTRA-ARTERIAL CHEMOTHERAPY ON HERPES SIMPLEX ANTIBODY LEVELS IN PATIENTS WITH HEAD AND NECK CARCINOMA

Harker, G. J., Hunt, J., Stephens, F. O., Sydney Hospital, Surgical Oncology Unit, *Macquarie St., Sydney, N.S.W. 2000, Australia*

Squamous cell carcinoma of the head and neck has been associated with herpes simplex type-1 virus in epidemiologic and serologic studies. Carcinoma of the lip, for example, has occurred more frequently at sites of recurrent herpes infection than at other sites of the lip. Serum levels of immunoglobulins in the IgA class, induced in a human tissue culture line by HSV, have been found to be elevated in patients with squamous carcinoma of the head and neck, as compared to patients with nonsquamous lesions and normal adults. In head and neck carcinoma, therefore, evidence for tumour-associated antigens that are induced by HSV provokes the speculation that the increases in IgA may be elicited by HSV-induced antigens. If determinations of such specificity exist, it may give significance to these elevations that would be useful in diagnosis, treatment, and monitoring of clinical course after treatment.

It is of interest, therefore, to evaluate such antibody levels as a baseline for patients with squamous cell carcinomas of the head and neck, and progressive estimations during intra-arterial chemotherapy and follow-up. A sensitive immunofluorescence technique with specificity for serum antibodies to HSV-induced cell membrane antigens is used: the serum level of these antibodies in each immunoglobulin class is estimated. Control groups of smoking and nonsmoking volunteers and a group with nonsquamous malignancies are being evaluated at present. When these studies are finalized, results will be published.

212. INTRA-ARTERIAL CHEMOTHERAPY IN ADVANCED HEAD AND NECK CANCER

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OBJECTIVE: To evaluate the role of intra-arterial chemotherapy in advanced head and neck cancer.

APPROACH: Sixty percent of cases attending the department are head and neck cancer patients. Of those, more than 50 percent are in advanced state at the time of reporting. These cases will be divided into two groups. One group will be treated by radiotherapy and the second group by intra-arterial chemotherapy by superficial temporal catheterization. The catheter will be located by arteriography and by intermittent chemotherapy plus radiotherapy. Tumor response, recurrence, complications and the quality and quantity of survival will be analyzed.

213. INTRAARTERIAL CIS-PLATINUM CHEMOTHERAPY PROTOCOL

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The purpose of this study is to further evaluate the activity of cis-platinum given intraarterially or intravenously in patients with head and neck cancers and to define the dose-response relationships of intraarterial cis-platinum.

Patients will be randomized between intraarterial or intravenous cis-platinum administration and evaluated for response rate and duration. Patients with colon cancer metastatic to the liver will have increasing doses of intraarterial cis-platinum to obtain the dose response curve.

To date three patients have been entered into the study. Two of those patients have responded and one is too early to evaluate.

214. THE USE OF INTRAVENOUS CYCLOPHOSPHAMIDE AND OTHER CYTOTOXIC DRUGS IN TREATMENT OF JAW LYMPHOMA

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OBJECTIVE: To determine the immediate and long-term effects of intravenous cyclophosphamide and other cytotoxic drugs on a limited number of cases of jaw lymphoma. The objectives will be determined by observing the differences in response rates and duration of remission in cases at early stages or in advanced cases with visceral metastasis. We would also like to determine why a tumor which is histologically similar to Burkitt's lymphoma does not respond clinically and therapeutically in the same way.

215. HUMAN LEUKOCYTE TREATMENT OF PATIENTS WITH VARIOUS MALIGNANT DISEASES

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Continuation of the clinical trial of interferon treatment for osteosarcoma: Patients admitted to the Karolinska Hospital since 1971 are all receiving interferon. Prognostic factors, metastases and survival compared to a concurrent control group consisting of all the other cases of osteosarcoma treated in Sweden during the same time. At present the frequency of metastases is about 50 percent in the interferon treated group as compared to the control group. A similar difference is obtained as regards survival.

A pilot study is done on juvenile laryngeal papilloma where patients exhibiting progressing tumor growth are treated with interferon. Regression has been demonstrated in 7 so treated cases. Upon removal of interferon progression again occurred. Regression has again been demonstrated after resumption of interferon administration.

Myeloma pilot study: Interferon has been shown to cause regression of multiple myeloma, even complete remissions. A pilot study is now continuing including also melphalan resistant myeloma cases.

A randomized study on multiple myeloma has been initiated where interferon therapy is compared to conventional melphalan-prednisolone treatment.

Studies of the effect of interferon therapy on malignant melanoma and ovarian cancer are to be initiated.

216. CHEMOTHERAPY IN THE TREATMENT OF METASTATIC OR RECURRENT CARCINOMA OF THE HEAD AND NECK

Schaefer, S. D., Middleton, R., Frenkel, E., Sudderth, J., Sheehan, R., Graham, M., Graham, H., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *4500 S. Lancaster Rd., Dallas, Texas,* 75216, United States of America

Patients with metastatic or recurrent carcinoma of the head and neck will receive cis-diamminedichloroplatinum (100 mg/m2 over 16 hours followed by an additional 24 hrs. of vigorously administered intravenous fluids) every 21 days until there is no evidence of disease, failure of response of the tumor or renal toxicity as defined by clearance of less than 50 ml per minute. Over the past year 7 patients have been entered into this protocol and 4 of these patients are now deceased. Three patients had an initial response to administration of platinum greater than 50%, with 2 of these patients still alive at this time. Two patients had a less than 50% reduction in their tumor mass after platinum and the remaining patients had no discernible response or died within one month after receiving platinum.

217. PILOT STUDY OF DIBROMODULCITOL IN SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

Williams, S. D., Einhorn, L. H., Stevens, E., Bond, W. H., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *1481 W. 10th St., Indianapolis, Indiana,* 46202, United States of America

Patients with advanced recurrent or metastatic squamous carcinoma not amenable to surgery or radiation therapy who have failed initial chemotherapy will be treated with Dibromodulcitol as a single agent. They will be evaluated for response and toxicity.

To date, only one patient has been entered into the study. The study continues but no conclusions are yet warranted. Toxicity has been acceptable.

218. CHEMOTHERAPY OF RECURRENT HEAD AND NECK CANCER

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Epidermoid cancer of head and neck sites is a common affliction in the V.A. population, affecting primarily heavy smokers and drinkers. Early lesions can be treated satisfactorily by conventional means, but many patients present with advanced disease, and recurrence and/or metastasis is then frequent.

Recurrent head and neck cancer carries a dismal prognosis. Retreatment by surgery or radiation is usually not feasible. Chemotherapy has been disappointing; although fair response rates can be achieved, notably with methotrexate, response durations rarely exceed six months.

A new agent, cis-platinum, has recently shown promise in head and neck cancer. This prospective study proposes to randomly allocate patients with recurrent disease into two groups, one receiving methotrexate and the other cis-platinum. Treatment regimens are conventional. Response rate (complete, partial, and non-response), response duration, and duration of survival will be measured for each group.

219. THE USE OF METHYL-G IN RECURRENT TUMORS OF THE HEAD AND NECK

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This is a pilot study designed to test the activity of Methyl-G in patients with cancers of the head and neck which have recurred following the standard treatment with surgery, radiation therapy and chemotherapy. One patient has been treated in this institution. It is too early to assess any activity at this time.

220. ECOG 2379 PHASE II STUDY OF NEW AGENTS IN THE TREATMENT OF ADVANCED CANCER OF THE HEAD AND NECK

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This study is a cooperative study of the Eastern Cooperative Oncology Group.

The objectives of this study are to determine the activity of new agents in the treatment of head and neck cancer. Patients selected for this study will be patients who have failed standard therapy with surgery, radiation, and chemotherapy and who are not eligible for ECOG Protocol of a higher priority.

Patients will be assigned at random to one of two agents. As patient accrual is met, new agents will be added. The current drugs under consideration are MGBG 600 mg/m2 IV weekly x 2 weeks escalated to 700 mg/m2 IV in the third week and thereafter; PALA 3.75 g/m2 IV q week.

221. SWOG 7860, EVALUATION OF MGBG IN SOLID TUMORS AND REFRACTORY HEMATOLOGIC MALIGNANCIES

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SWOG 7860 - The objectives of this study are to determine response rate and remission duration with primary weekly intravenous therapy using MBGB in patients with advanced esophageal, breast, pancreatic, colorectal, and head and neck carcinomas and lymphoma; and to define the qualitative and quantitative toxicity of this regimen.

MBGB is intended as initial chemotherapy for patients with inoperable or disseminated renal, esophageal, and pancreatic carcinoma. It is intended for use in patients with other forms of advanced malignancy (breast, head and neck, colorectal, lymphoma and multiple myeloma) if their disease has become progressive after initial chemotherapy and they are not candidates for SWOG studies of higher priority. The dose of MBFB is 500 mg/m2 to be given as an intravenous infusion in D5W or normal saline over no less than 30 minutes, into a freely running IV weekly. One hundred and nine patients with advanced malignancy, refractory to conventional therapy, were treated with a weekly schedule of methyl-GAG. Ninety-one patients (83%) were less than fully ambulatory. Sixty-five patients were fully evaluable for response. There were two complete and nine partial responses. An additional nine patients had objective tumor regressions and were classified as improved. The median duration of response was 5 months. Toxic effects were primarily mucositis (17 patients) and nausea and vomiting (14 patients). Sixty-seven patients had no manifestations of drug toxicity. Responses observed in a wide variety of solid tumors warrant further clinical trials.

222. EVALUATION OF DHAD IN ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK, PHASE II

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Patients must have a histologically confirmed diagnosis of squamous cell carcinoma of the head or neck region. Patients must have been given an adequate trial with disease progression on Southwest Oncology Group protocols of higher priority in order to be eligible. All patients must have measurable disease and a minimum life expectancy of three months.

The objective is to determine the response rate and remission duration in patients with advanced squamous cell carcinoma of the head and neck treated with DHAD used in a single dose every three weeks.

223. A PHASE I/II STUDY OF 4'EPIADRIAMYCIN

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This trial involves the administration of a new agent, 4'epiadriamycin (EADM) - a close analogue of the known agent, adriamycin (ADM) - to patients with melanoma, colorectal or renal carcinoma or head and neck cancer.

The objectives of this study are to determine limiting dose and toxicities to assess activity of the drug in patients with the above mentioned cancers; to determine its cardiotoxic potential and pharmacokinetics; and finally to assess the activity of this compound in patients who have failed therapy with ADM.

The drug will be administered through femoral vein catheters and will start at a dose of 60 mg/m2. If tolerated, the dose will be escalated in each successive cycle to 75 mg/m2 and then 90 mg/m2. Patients will be treated every 3 weeks and will be carefully monitored at each administration, both for physical signs and symptoms and for changes in laboratory values. They will also receive interval physical and laboratory examinations to determine the extent of toxicity.

224. PHASE II EVALUATION OF VINDESINE IN ADENOCARCINOMA OF THE LUNG AND HEAD AND NECK CANCER

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Vindesine, a semisynthetic vinblastine derivative, has been extensively evaluated in clinical trials in the past three years. Partial responses to this drug have been noted in patients with various types of malignancies.

The favorable results of previous clinical trials have prompted the interest in using vindesine in Phase II clinical trials for patients with adenocarcinoma of the lung having no previous treatment; and patients with head and neck cancer who have failed surgery and/or radiotherapy treatments.

Patients from the general medical oncology population (Audie L. Murphy VA Hospital/Bexar County Hospital District) after appropriate pre-treatment measurements (physical, laboratory assessments) will receive 3mg/m2/wk IV push. Patients will be monitored for toxicity and antitumor effects of the drug.

225. SWOG-7934, EVALUATION OF ACRIDINYLAMINOMETHANSESULFON-M-ANISIDIDE (AMSA) IN METASTATIC SQUAMOUS CARCINOMA OF THE HEAD AND NECK, PHASE II

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It is the purpose of this study to determine the anti-tumor activity of m-AMSA in a single dose schedule in patients with metastatic squamous carcinoma of the head and neck who have failed on higher priority treatment protocols. m-AMSA is a drug which has suggestive activity in preliminary studies in head and neck cancer. Anti-tumor activity will be determined by response rate and duration of response. In addition, the study is designed to determine the nature and degree of toxicity of this drug in patients with head and neck cancer.

226. A RANDOMIZED PHASE III STUDY OF PLATINUM WITH OR WITHOUT METHOTREXATE FOR RECURRENT SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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OBJECTIVE: The objectives of NCOG Protocol 7H81 are 1) to compare the effects of combination chemotherapy with those of single agent chemotherapy on complete and partial response rate, on duration of response and on survival and 2) to compare acute and chronic toxicities associated with these treatment regimens.

RESEARCH PLAN: Using estimates of annual patient accrual from institutions within the group, total accrual over a two year period is expected to be 150-185 with 75-92 per treatment arm. An additional year will be required for patient follow-up. The data gathered will be analyzed at four-month intervals.

METHODOLOGY: Patients judged eligible for the study will receive treatment assignment according to a modification of the forced balancing (adaptive randomization) precedure of Efron with regard to institution and the other stratification varibles. Response and toxicity rates will be analyzed by multiple logistic methods. The method of analysis for disease-free intervals and survival time will be patterned after the Cox actuarial analysis for censored survival data with covariates identifying the two treatment groups.

FINDINGS: To date, overall objective response rates are 17 percent and 38 percent. The median times to failures are 56 days and 84 days. In the platinum-only arm, there have been three grade 3 hematologic toxicities, eight grade 3 non-hematologic toxicities, and one grade 4 non-hematologic toxicity. There have been no toxic deaths on this arm. In the platinum-plus-methotrexate arm, there have been six grade 3 hematologic toxicities, two grade 4 hematologic toxicites, and eight grade 3 non-hematologic toxicities. One toxic death due to infection occurred on this arm.

227. ORAL RETINOIDS IN THE TREATMENT OF LEUKOPLAKIA

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No summary has been provided to the Smithsonian Science Information Exchange.

228. COMBINED CHEMOTHERAPY IN HEAD AND NECK CANCER (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

229. THE VALUE OF BLEOMYCIN PLUS DBD THERAPY IN THE TREATMENT OF HEAD AND NECK TUMOR PATIENTS

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This trial was begun on November 14, 1977. Since that time 19 randomized patients have entered the study. Twelve patients have been treated by bleomycin plus DBD and 7 received bleomycin only. Patients who were accepted for the trial had been treated earlier by irradiation and/or surgery, or had recurrent disease not amenable to these therapies.

DOSES: Bleomycin i.m. 15 mg/square meter, three times weekly and DBD 400 mg/square meter once a week. The period of the treatment is eight weeks. During the treatment blood count and pulmonary status must be controlled. The total dose of the bleomycin reached 400-672 mg and that of DBD 3,300-5,600 mg. Reversible side effects only were observed after the treatment. Eleven regressions have been observed so far. We plan to treat 60 patients.

230. EVALUATION OF METHOTREXATE AND INTERMITTENT LOW-DOSE CIS-PLATINUM IN THE TREATMENT OF RECURRENT HEAD AND NECK CANCER (ABBREV)

Schaefer, S. D., Sudderth, J., Carder, H. M., Strauss, J., Middleton, R., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Div. of Otolaryngology, *4500 S. Lancaster Rd., Dallas, Texas*, 75216, United States of America

Squamous cell carcinomas of the head and neck region comprise approximately 5% of all malignancies in this country. Once the potential for further local treatment with surgery or radiation has been exhausted, there arises an urgent need for developing an effective means of providing further symptomatic palliation and prolongation of a reasonable quality of life in these patients. Over the past decade, a number of therapeutic agents, singly or in combination, have been evaluated toward achieving this goal. Despite risks due to a nutritionally debilitated condition and enhanced toxicity related to poor general condition and prior treatment, methotrexate has emerged as a predictively effective agent in a significant portion of patients. More recently, cis-platinum (DDP) has been found to be another effective agent in the treatment of recurrent and previously untreated head and neck carcinomas.

We propose to compare, in a prospective, randomized manner, the relative efficacy and toxicity of treatment with weekly IV methotrexate and intermittent low-dose cis-platinum in patients with recurrent (after surgery and radiation) squamous cell carcinoma of the head and neck. Patients will be stratified as to performance status and site within the head and neck. Two treatment arms will consist of methotrexate 40 mg/m2 IV once a week to progress to total dose of 60 mg/m2 versus cis-platinum 50 mg/m2 via 6-hour infusion. Platinum will be given on days 1 and 8 of every month. All patients will voluntarily be entered into this study after giving an informed consent and will have the right to withdraw at any time.

231. MTX/BLM/DDP IN EPIDERMOID HEAD AND NECK CANCER

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OBJECTIVE: To assess the responsiveness of advanced or relapsing epidermoid head and neck tumors to a simultaneous combination BLM/MTX/DDP.

APPROACH: Non-randomized open pilot study. Measurable tumors, mostly previously irradiated or surgically treated patients.

BLM: 10 mg/m2 i.v. days 1,3,5.
MTX: 30 mg/m2 i.v. day 1.
DDP: 20 mg/m2 i.v. days 3,4,5.

PROGRESS: Seven patients entered. No preliminary report.

232. SECSG PROTOCOL 79 HN 356 FOR STAGE III AND IV EPIDERMOID CARCINOMA OF ORAL CAVITY OF HYPOPHARYNX AND LARYNX

Williams, S. D., Bond, W. H., Einhorn, L. H., Stevens, E., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Service, *1481 W. 10th St., Indianapolis, Indiana*, 46202, United States of America

Patients with newly diagnosed stage III or stage IV epidermoid carcinoma of the oral cavity, hypopharynx or larynx, will be randomized to receive or not to receive pre-operative chemotherapy. Patients with T4N3 lesions are considered too advanced for this protocol and are not eligible. Chemotherapy will consist of methotrexate 70 mg/M2 I.V. push every six hours for four doses followed by leucovorin factor rescue consisting of leucovorin factor, 6 mg intravenously every six hours for nine doses. Bleomycin will be given in a dose of 20 mg intravenously every seven days for six doses. Cis-platinum 2 mg/kg will be given by I.V. drip on day three, and repeated on day 24. If no toxicity occurs, the methotrexate dose will be escalated to 140 mg/M2 and given on day 21, followed again by folinic acid rescue. Patient will then be evaluated for surgery. Those patients demonstrating metastatic disease or unresectable lesions will be taken of the study. Following surgery, patients will receive radiation therapy consisting of 5,500 to 6,000 rads over five to seven weeks. Patients randomized to receive no chemotherapy will receive identical surgical techniques and radiation therapy. The two groups will be compared for disease-free survival, toxicity and complications. The response rate to the combination chemotherapy regimen prior to surgery will be evaluated. The toxicity is acceptable. The study continues. Patient accrual has not been met.

233. PROTOCOL FOR PATIENTS WITH ADVANCED HEAD AND NECK CANCER WITHOUT PRIOR CHEMOTHERAPY

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Twenty-six patients with advanced head and neck cancer, 22 of whom had failed prior surgery and/or radiotherapy, were treated with a combination regimen of cis-diamminedichoroplatinum II, bleomycin and methotrexate. There were no complete responses. Nine patients achieved a partial response (35%). Three of the four (75%) patients without prior therapy achieved a partial response while only 6 of the 22 patients (27%) with prior surgery and/or radiation therapy obtained a partial response. The median response duration was 3 months. Patients with a partial response did not live significantly longer than those who did not respond. Toxic reactions were frequent: there were three episodes of sepsis secondary to leukopenia and 2 cases of bleomycin pulmonary toxicity. Mucositis was noted in 40% and nausea and vomiting in 60% of patients. We conclude that this triple drug regimen has little value in the treatment of patients with advanced squamous cell carcinoma of the head and neck who have failed prior surgery and radiotherapy.

234. CHEMOTHERAPY FOR CARCINOMA OF THE HEAD AND NECK

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Advanced squamous cell carcinoma of the head and neck or esophagus have a very poor five-year survival despite aggressive local treatment with surgery, radiotherapy or both. Many such patients die of metastatic disease. Therefore, a pilot trial of aggressive combination chemotherapy was warranted to determine if an improved response rate or survival can be obtained. Bleomycin, cis-platinum II with hydration, and high-dose methotrexate with citrovorum rescue are agents with activity in these tumors. Thirty-three patients were treated with combinations of these agents. Twenty-six received a three-drug combination and 7 patients received only DDP and bleomycin. There was a 73% response rate in previously untreated patients with 4 complete and 12 partial responses, and a 55% response rate in previously treated patients, all PR's. Duration of response to a single course of chemotherapy is 8-12 weeks. Toxicity included vomiting, alopecia, leukopenia, thrombocytopenia, mucositis and elevated serum creatinine. There were 2 drug-related deaths. Among the 22 responders, 12 had surgery, 5 had subsequent radiotherapy. Among the 11 failures to therapy, 3 had surgery and 1 had radiotherapy. Twelve patients received no local therapy. Similar studies are now under way in cooperative groups.

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235. STUDY OF CIS-DIAMMINEDICHLOROPLATINUM PLUS VINBLASTINE PLUS BLEOMYCIN VS. METHOTREXATE IN PATIENTS WITH SQUAMOUS HEAD & NECK CANCER (ABBREV)

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This is an attempt to determine whether a combination of chemotherapeutic agents is advantageous over methotrexate alone in the treatment of metastatic or recurrent squamous cell carcinoma of the head and neck. The objective is to study whether methotrexate in high dose is better than cis-platinum, vinblastine and bleomycin in combination. Patients will then be randomized to either a high dose of methotrexate or a combination of cis-platinum, vinblastine and bleomycin. It is hoped that as a result of this study we will be able to determine whether a combination of some of the more active agents other than methotrexate has any advantage over methotrexate given in high dose.

236. TREATMENT OF ADVANCED OR RECURRENT CARCINOMA OF THE HEAD AND NECK

Spaulding, M. B., Sanani, S., Klotch, D., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Medical Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

This protocol is designed to test the combination of drugs, cis-diamminedichloroplatinum, bleomycin and vincristine, in the treatment of patients with advanced carcinoma of the head and neck. Only previously untreated patients received this protocol during the preceding year. There were 17 patients who received two courses of this chemotherapy pre-operatively. The chemotherapy was tolerated well with no major toxicity. All but one patient had a greater than 50% response to the chemotherapy following two courses of treatment. Evaluation to date would show that the time to recurrence in these advanced lesions has been significantly reduced by pre-operative chemotherapy. Whether there is survival benefit will be determined over the upcoming years.

237. TREATMENT OF ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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This is a randomized study for treatment of advanced (inoperable) carcinoma of head and neck regions. The past studies using methotrexate in small doses, high dose methotrexate with citrovorum factor (leucovorin) rescue, cis-platinum, bleomycin and combinations thereof, produced some encouraging results. However, the control of the disease has been usually short. This study employs the best available modalities of treatment. This randomized study uses two arms. One arm consists of high dose methotrexate with vincristine priming and leucovorin rescue administered in meticulously monitored manner to avoid toxicity. The second arm uses the introduction of cis-platinum in the cycle of high dose methotrexate with leucovorin rescue in an attempt to seek any possible improvement of this latter mode of therapy. In addition, cis-platinum is used in patients with stage III and IV carcinoma of the head and neck who had previous chemotherapy, including methotrexate. In such patients, there is no randomization since thee is no alternative therapeutic course for the treatment of such patients. The study is projected on a restricted randomization to include 30 patients; afterwards we should be able to determine whether or not cis-platinum can improve the results of high dose methotrexate therapy in patients with stage III and IV carcinoma of the head and neck. Careful monitoring of the hematologic, gastrointestinal and possible renal toxicity assures us that no undue side effects will be encountered. If, however, such side effects should occur, it is stipulated that the treatment will be discontinued and a palliative therapeutic approach will be instituted.

238. ADJUVANT THERAPY OF HIGH RISK HEAD AND NECK CARCINOMA

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Pilot trials of Cytoxan, 5-fluorouracil, methotrexate and bleomycin had in combination given complete or partial responses in 8 of 13 cases of advanced head and neck carcinoma.

PROJECT OBJECTIVES: To determine if the addition of B-CMF prior to conventional therapy (irradiation and surgery) could improve length of remission and survival; to determine prognostic factors, site and interval of recurrent disease; to quantitate toxicities of the chemotherapy.

PLAN: To perform a prospective, randomized and stratified investigation of basal chemotherapy for patients with advanced head and neck carcinoma.

METHOD: Patients have been randomized to receive either conventional therapy alone or chemotherapy in addition to conventional therapy. Chemotherapy has been given over 5 days/course with de-escalation in association with patient condition and intolerance. Surgical and radiation therapy have been performed according to guidelines established by the Medical College of Wisconsin.

RESULTS TO DATE: Forty nine (49) patients have been randomized (27 at VAMC), 24 receiving chemotherapy. For reasons which remain unclear, complete remissions have not been seen. Two patients have had complete remissions at the primary site with little or no improvement in the regional lymph node metastases. Fifteen have had a partial response or have shown improvement. There were 5 non-responders. One patient was unevaluable due to lack of compliance, and one is currently under treatment. Length of survival has been poor in both groups, though a good response to chemotherapy appears to be a short-term prognostic factor. Patients have tolerated chemotherapy well without unexpected or life-threatening sequellae.

239. CALGB 8001 - BLEOMYCIN INFUSION FOLLOWED BY CYCLOPHOSPHAMIDE, METHOTREXATE PLUS 5-FLUOROURACIL FOR HEAD AND NECK CANCER (ABBREV)

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Advanced head and neck carcinoma is refractory to chemotherapy with most currently available agents. Initial case reports of combination chemotherapy of constant infusion bleomycin with cyclophosphamide, methotrexate and 5-fluorouracil pulse suggest this regimen may be effective in advanced head and neck malignancy.

purpose: Pilot study to determine efficacy of bleomycin infusion followed by cyclophosphamide, methotrexate and 5-fluorouracil pulse in advanced head and neck malignancies.

PLAN: Patients with advanced head and neck malignancies receive continuous infusion of bleomycin 7.5 mg/M2 per day days 1-5. Pulse injection of cyclophosphamide 300 mg/M2; methotrexate 30 mg/M2, and 5-fluorouracil 300mg/M2 is given IV on day 5. Cycle is repeated every 28 days. Dose is adjusted for bone marrow suppression, pulmonary toxicity, cystitis, mucositis, liver or renal toxicity. Therapy continues until disease progresses.

NOTE: This study is now a MCV, Division of Medical Oncology, pilot; data on tumor response is analyzed at MCV.

240. OMRF 7709 - CYCLIC CHEMOTHERAPY FOR ADVANCED CARCINOMA OF THE HEAD AND NECK

Bottomley, R. H., Grozea, P. N., Murray, J. L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology Section, *921 N.E. 13th St., Oklahoma City, Oklahoma,* 73104, United States of America

OBJECTIVES: The purpose of this study is to determine the response rate of squamous cell carcinoma of the head and neck to a cyclic combination chemotherapy program consisting of courses of bleomycin and methotrexate alternating with courses of adriamycin and cis-platinum.

Treatment will begin with bleomycin and methotrexate given in the vein over a 24-hour period. The patient will be hospitalized for this treatment. On day 15, the patient will receive treatment with adriamycin and cis-platinum given in the vein with mannitol in approximately 1 quart of dextrose and water. This will be done on an out-patient basis and will take two hours. Starting with day 36 this course of therapy will be repeated until regression of the disease occurs or until significant toxicity is encountered.

There have been 15 V.A. patients registered on this protocol, with 4 patients remaining on protocol.

Toxicities consisted of leukopenia, nausea, vomiting, anorexia and alopecia.

241. A KINETICALLY DESIGNED COMBINATION CHEMOTHERAPY PROTOCOL FOR ADVANCED SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK (ABBREV)

Hill, B. T., Price, L. A., Shaw, H. J., Dalley, V. M., Imperial Cancer Research Fund, Cellular Chemotherapy Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

We have developed a safe and effective method of administering combination chemotherapy and used it to treat T3 and T4 squamous cell carcinomas of the head and neck. In this trial 116 assessable patients were divided into two groups: Group 1 - new patients receiving chemotherapy before planned radiotherapy or surgery. Group 2 -patients with recurrent previously treated disease. The protocol, given over 26 hours, contains vincristine, bleomycin, methotrexate, hydrocortisone and 5-fluorouracil, with a folinic acid rescue. The objective response rates of 75 percent in Group 1 but only 50 percent in Group 2 patients and the lack of significant adverse side effects were reported previously (ICRF Scientific Report 1978 - report 18).

Crude survival data now show that 50 percent of Group 1 patients were alive at 2 years compared with a 25 percent survival rate in a historically matched control group. Failure to respond to initial chemotheapy is a bad prognostic sign since no non-responders survived 2 years. In Group 2, where prior radiotherapy was the main factor in reducing response to chemotherapy, no survival benefit was obtained from chemotherapy, with median survivals of 320 or 250 days in responders versus non-responders. Alternative chemotherapy is now being considered for these patients. However, the effectiveness and safety of this protocol in previously untreated patients has led to its incorporation into randomized prospective controlled studies by groups in London and Liverpool, to see whether this approach can increase the cure rate in this group of diseases or at least increase survival with less mutilation.

242. TREATMENT OF ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

Goffin, F. B., Broach, J. E., Odom, J., Waycaster, M., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Head & Neck Service, *Mountain Home, Johnson City, Tennessee,* 37684, United States of America

PROJECT OBJECTIVES: 1. To treat advanced squamous cell carcinoma of the Head and Neck with a 5 drug regime according to Protocol No. 99179 of the Piedmont Oncology Group. This employs hydroxyurea, methotrexate, bleomycin, Cytoxan, and cis-platinum. This modality is used in attempt a) to render T4 lesions palliative after radiation therapy or b) to reduce T4 to T3 to render them resectable. 2. To compare 5 drug regimen with standard single drug, methotrexate.

PLAN: Patients with T4 disease following traditional and palliative cobalt or patients with non-resectable radiation failures are placed on protocol.

METHOD: As stated in plan.

CLINICAL RELATIONSHIP: This research is relevant to the high incidence of advanced head and neck carcinomas in the Mountain Home drawing area.

243. ADJUVANT CHEMOTHERAPY IN HEAD AND NECK CARCINOMA

Carter, S. K., Northern California Cancer Program Inc., *770 Welch Rd., Suite 190, Palo Alto, California,* 94304, United States of America

OBJECTIVE: Test the effects of high dose chemotherapy before surgery on head and neck squamous carcinoma.

244. CHEMOTHERAPY IN HEAD AND NECK SQUAMOUS CARCINOMA

Kramer, S., American College of Radiology, *925 Chestnut St., Philadelphia, Pennsylvania,* 19107, United States of America

OBJECTIVE: Test the effects of high dose chemotherapy before surgery on head and neck squamous carcinoma.

245. CHEMOTHERAPY IN HEAD AND NECK SQUAMOUS CARCINOMA

Endicott, J. N., State University System of Florida, University of South Florida, School of Medicine, Dept. of Surgery, *4202 Fowler Ave., Tampa, Florida,* 33620, United States of America

OBJECTIVE: Test the effects of high dose chemotherapy before surgery on head and neck squamous carcinoma.

246. CHEMOTHERAPY TRIAL IN HEAD AND NECK SQUAMOUS CARCINOMA

Bailey, B. J., University of Texas, Medical Branch at Galveston, School of Medicine, Dept. of Otolaryngology, *300 University Blvd., Galveston, Texas*, 77550, United States of America

OBJECTIVE: Test the effects of high dose chemotherapy before surgery on head and neck squamous carcinoma.

247. CHEMOTHERAPY IN HEAD AND NECK SQUAMOUS CARCINOMA

Shumrick, D. A., University of Cincinnati, School of Medicine, Dept. of Otolaryngology & Maxillofacial Surgery, *Eden & Bethesda Aves., Cincinnati, Ohio*, 45221, United States of America

OBJECTIVE: Test the effects of high dose chemotherapy before surgery on head and neck squamous carcinoma.

248. CHEMOTHERAPY IN HEAD AND NECK SQUAMOUS CARCINOMA

Elias, E. G., University of Maryland, Baltimore Professional Schools, School of Medicine, Dept. of Surgery, *655 W. Baltimore St., Baltimore, Maryland*, 21201, United States of America

OBJECTIVE: Test the effects of high dose chemotherapy before surgery on head and neck squamous carcinoma.

249. CHEMOTHERAPY IN HEAD AND NECK SQUAMOUS CARCINOMA

Strong, E. W., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

OBJECTIVE: Test the effects of high dose chemotherapy before surgery on head and neck squamous carcinoma.

250. CHEMOTHERAPY IN HEAD AND NECK SQUAMOUS CARCINOMA

Krause, C., University of Michigan, Ann Arbor Campus, Medical School, Dept. of Otorhinolaryngology, *1335 E. Catherine St., Ann Arbor, Michigan*, 48104, United States of America

OBJECTIVE: Test the effects of high dose chemotherapy before surgery on head and neck squamous carcinoma.

251. ADJUVANT CHEMOTHERAPY OF OPERABLE HEAD AND NECK SQUAMOUS CARCINOMAS (HUMAN)

Krause, C. J., University of Michigan, Ann Arbor Campus, Medical School, Dept. of Otorhinolaryngology, *1335 E. Catherine St., Ann Arbor, Michigan*, 48104, United States of America

This is part of a broader project. A summary of this subproject is not available.

252. ADJUVANT CHEMOTHERAPY IN EPIDERMOID CARCINOMA OF HEAD AND NECK (HUMAN)

Capizzi, R. L., University of North Carolina, Chapel Hill Campus, School of Medicine, Dept. of Medicine/Pharmacology, *Manning Dr., Chapel Hill, North Carolina*, 27514, United States of America

This is part of a broader project. A summary of this subproject is not available.

C. COMBINED CHEMOTHERAPY AND RADIOTHERAPY

253. CLINICAL TRIALS ON DIFFERENT MODES OF TREATMENTS OF ORAL CANCER, AND CANCER OF THE ESOPHAGUS AND BREAST

Mukherjee, A. K., Medical College Hospitals, Dept. of Radiotherapy & Nuclear Medicine, *Chewayoor Kerala, Calcutta 700073, West Bengal, India*

OBJECTIVES: 1) Clinical trials on treatment of oral cancers of different types by the following three modes of combination treatments: a) chemotherapy in suitable combinations followed by radiotherapy; b) chemotherapy in suitable combinations followed by surgery; and c) chemotherapy in suitable combinations followed by both surgery and radiotherapy. 2) Treatment of cancer of the esophagus with chemotherapy in different combinations followed by radiotherapy. 3) Treatment of cancer of the breast and differential variations of standard modes of treatment at different stages of the disease.

APPROACH: For 1, 2 and 3, different combinations of treatment are given to the patients and their clinical results are being followed up.

PROGRESS: The clinical results are being studied and more data are being collected.

254. CLINICAL TRIAL TO EVALUATE RT PLUS BLM PLUS CDDP, RT PLUS BLM AND RT PLUS CDDP IN ADVANCED ORAL CANCERS

Shanta, V., Krishnamurthi, S., Sastry, D. V., Vasanthan, A., Krishnamurthi, R., Sasikala, K., Sagar, T. G., Cancer Inst., Clinical Oncology Research Unit, *Adyar, Madras 600020, Madras, India*

OBJECTIVE: To evaluate the combination of CDDP plus RT plus BLM versus CDDP plus RT and BLM plus RT in T3, T4 oral squamous cell carcinomas histologically confirmed. This is a three-arm randomized controlled clinical trial. The groups are constructed under well-defined standardized criteria of eligibility and by sex using the sealed envelope technique.

The approach in this trial is twofold. One approach involves comparison of the relative values of CDDP and BLM when used in combination with radiation. The second is to explore the possibility of a synergistic action of the drugs in oral cancer. BLM is known to be most effective in the G2 and M phases of the generation cycle whereas the mechanism of CDDP is not fully known. Criteria of response are: 1) Short-term - Favorable response is total clinical healing of the tumor within the volume of radiation at 8 weeks after end of therapy. 2) Long-term - a) Recurrence-free rate within the volume of irradiation at 3 and 5 years; b) survival NED at 3 and 5 years. The randomization and evaluation are blind and by code.

A total of 90 cases will enter the trial, 30 in each group - 15 males and 15 females.

This trial has commenced and is likely to continue for two years.

255. CONTROLLED CLINICAL TRIAL - EVALUATION OF PLM PLUS RADIATION VERSUS BLM PLUS RADIATION IN T3, T4 ORAL SQUAMOUS CELL CARCINOMAS

Shanta, V., Krishnamurthi, S., Sastry, D. V., Krishnamurthi, R., Sasikala, K., Cancer Inst., Clinical Oncology Research Unit, *Adyar, Madras 600020, Madras, India*

OBJECTIVE: To evaluate Pepleomycin versus Bleomycin as a potentiating agent in the radiotherapy of oral squamous cell carcinomas.

APPROACH: A concurrent randomized, controlled trial in T3 and T4 oral squamous cell carcinomas, previously untreated (except for histological confirmation), was conducted. The trial groups were randomized on the basis of defined criteria of eligibility and by sex, using the sealed envelope technique. The therapy and evaluation were blind and run by code. Sixty-four patients entered the trial - 32 study cases and 32 controls. The criteria of response were: 1) Favorable response, i.e., total clinical healing of the tumor within the volume of irradiation at 8 weeks after end of therapy (short-term). 2) Recurrence-free rate within the volume of irradiation at 3 and 5 years (long-term). 3) Survival NED at 3 and 5 years.

PROGRESS: Only a short-term evlauation is possible at the present time, viz. 'favorable response', and the results are as follows: Number of patients treated, number of patients available for evaluation, number of favorable responses, and percentage in the study group (RT plus PEP) and in the control group (RT plus BLM) - 32, 28, 17, 60.7 percent and 32, 30, 21, 70.0 percent, respectively.

Apparently the RT plus BLM combination proved slightly superior to the RT plus Pepleomycin combination. There were no differences in morbidity between the two drugs, and side effects consisted mainly of oral mucositis. However, as a result of past experience very few patients' mouths were dry and the mucosa was not atrophic. No pulmonary complications occurred.

256. CLINICAL TRIAL TO COMPARE RT PLUS CDDP, RT PLUS BLM AND RT ALONE IN SQUAMOUS CELL CARCINOMAS OF THE THRORACIC ESOPHAGUS

Shanta, V., Krishnamurthi, S., Sastry, D. V., Krishnamurthi, R., Vasanthan, A., Rangakumar, G., Cancer Inst., Clinical Oncology Research Unit, *Adyar, Madras 600020, Madras, India*

OBJECTIVE: To evaluate the effectiveness of high energy photon radiation therapy per se versus the combination of radiation therapy plus BLM and RT plus CDDP in squamous cell carcinomas of the thoracic esophagus.

All cases of histologically confirmed, previously untreated squamous cell carcinomas of the thoracic esophagus without evidence of juxta-regional metastases or remote metastases or clinical invasion of the myocardium or the thoracic aorta will be randomized presently into three groups by the sealed envelope technique. Sub-randomization by sex will also be done. Randomization and evaluation will be blind and by code.

A total of 120 cases will be entered in the trial. Criteria of response will be 1) Short-term: Favorable response - apparent total clinical healing of the lesion within the volume of irradiation at 8 weeks after end of radiation as established by radiology and fiber optic endoscopy. 2) Long-term: a) Recurrence-free rate within the volume of irradiation at 3 and 5 years. b) Survival NED at 3 and 5 years.

The project will continue for 3 years.

257. CLINICAL TRIAL - BLM PLUS HBO PLUS RT VERSUS BLM PLUS RT AND HBO PLUS RT IN THE TREATMENT OF T3, T4 ORAL SQUAMOUS CELL CARCINOMA

Shanta, V., Krishnamurthi, S., Sastry, D. V., Krishnamurthi, R., Vasanthan, A., Sharma, M., Cancer Inst., Clinical Oncology Research Unit, *Adyar, Madras 600020, Madras, India*

OBJECTIVE: To evaluate the relative values of the combination of HBO plus RT, BLM plus RT and HBO plus BLM plus RT in a concurrent, randomized controlled clinical trial in T3, T4 oral squamous cell carcinomas previously untreated and confirmed histologically.

APPROACH: The trial groups were constructed according to well-defined and standardized criteria of eligibility and by sex using the sealed envelope technique. The randomization and evaluation were blind and by code. The criteria of response were: 1. Short-term: Total clinical healing of the lesion within the volume of irradiation at 8 weeks after end of therapy. 2. Long-term: a) Recurrence-free rate within the volume or irradiation at 3 and 5 years; b) survival NED at 3-5 years.

PROGRESS: Eighty-four patients entered the trial, 28 in each group - 14 males and 14 females. Only a short-term evaluation is possible at the present time, and the results are as follows: Number of patients treated, number of patients available for evaluation, number of favorable responses, percentage in the code groups XYZ - 28, 25, 17, 68%; 28, 22, 13, 59%; and 28, 25, 8, 32%, respectively.

258. A PHASE I CLINICAL TRIAL OF RADIATION SENSITIZERS AND A STUDY OF SOME OTHER THERAPEUTIC FACTORS

Thomas, G. M., Bush, R. S., Cummings, B. J., Dembo, A. J., Harwood, A. R., Hill, R. P., Rauth, A. M., Rider, W. D., Whitmore, G. F., Ontario Cancer Inst., Dept. of Radiation Oncology, *500 Sherbourne St., Toronto, Ontario,* M4X 1K9, Canada

OBJECTIVE: This is a phase I clinical and pharmacological investigation of two drugs, metronidazole and misonidazole. These drugs have potential use in the clinical setting as hypoxic cell radiation sensitizers. As such they may improve local control and cure with radiation of patients with carcinomas.

Our objective is to document and quantitate the types of acute toxicities associated with the administration of these drugs to patients receiving conventional daily fractionated radiation therapy to the pelvis in patients with carcinoma of the cervix and to the head and neck in patients with carcinomas of the head and neck.

APPROACH: Groups of patients are being studied at escalating levels of daily drug dosage. This will enable us to determine the maximum daily drug dosage which can be safely administered to such patients. It will also allow us to determine whether further trials to measure the therapeutic efficacy of these agents are justified.

Detailed pharmacokinetic studies using high pressure liquid chromatography are being performed to enable correlation of acute toxicities with plasma and urine drug levels.

259. MISONIDAZOLE ADJUVANT TO RADIOTHERAPY IN HN CANCERS

Fazekas, J. T., Phillips, T., Marcial, V., Thomas Jefferson University, Jefferson Medical College, Dept. of Radiation Therapy & Nuclear Medicine, *1025 Walnut St., Philadelphia, Pennsylvania,* 19107, United States of America

This project has been approved by NCI under the usual RTOG mechanisms and has been active since 10/79. Approximately 80 patients have been entered into this phase III trial testing 'standard' X-ray therapy in T3/T4 squamous cancers of the HN area versus 'standard' X-ray therapy (slightly modified) and 2.0 gm/mm2 of Misonidazole once weekly for 6 weeks. The endpoints are local control/survival.

260. COMBINED TREATMENT WITH RADIATION AND TRIETHYLENETHIOPHOSPHORAMIDE (THIO-THEPA) IN ADVANCED CANCER OF TONGUE AND FLOOR OF MOUTH

Constantin, E., Gonzalez, R., Gaitan, A., Instituto Nacional de Cancerologia, Seccion Nacional de Cancerologia, *Apartado Aereo #17.158, Calle 1 No. 9-85, Bogota, DE, Colombia*

OBJECTIVE: To determine the effectiveness of combined treatment with radiation and cytostatics in advanced cancer of the tongue and floor of the mouth.

MATERIAL: Patients with advanced cancer of the tongue and floor of the mouth (T3, T4, and/or N3).

METHOD: Two series of 3,000 rads in 2 weeks (10 fractions) alternating with three series of triethylenethiophosphoramide (thio-TEPA), each series of 60 mg/m2 divided into 6 daily doses per cycle.

261. CHEMOTHERAPY IN THE TREATMENT OF INOPERABLE CARCINOMA OF THE HEAD AND NECK

Schaefer, S. D., Middleton, R., Frenkel, E., Sudderth, J., Sheehan, R., Graham, M., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *4500 S. Lancaster Rd., Dallas, Texas,* 75216, United States of America

The capacity of induction cytoreductive chemotherapy to improve control of advanced head and neck tumors by multimodality therapy was studied. Twenty-eight patients with inoperable and radical radiothrapy incurable advanced Stage IV tumors were treated with cis-platinum (DDP) as initial induction (100 mg/M2 - 16 hr. infusion on days 1 and 21) followed by radiation with 6500 rads to the primary and 5000 rads to the supraclavicular area given over 6 weeks. Eleven (39%) patients achieved a complete remission (CR) with a median disease free interval of 8 1/2 months, and 10 (35%) had an objective partial remission (PR). Of the 11 CR patients, 5 had subsequent radical neck dissection. Seven PR patients had total regression of the primary and with residual cervical nodal disease, underwent radical neck dissection with a disease free interval of 10 months. Surgery resulted in freedom from disease at the cervical site in all but 2 patients. Histologic study of the nodes demonstrated the unreliability of physical examination as a criteria of active nodal disease post-therapy. In 2 patients composite resection following initial therapy resulted in CR status. Of the 28 patients, there are 9 who are alive and disease free up to 18 months. Thus, cis-platinum induction chemotherapy enhances multimodality therapy and produces a subset of patients with complete remission and prolonged disease free survival. Presentation with neck involvement merits planned resection regardless of the subsequent clinical findings.

262. SWOG-7968, TREATMENT OF EARLY SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK WITH INITIAL SURGERY AND/OR RADIOTHERAPY FOLLOWED BY CHEMOTHERAPY

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas,* 78284, United States of America

This study is designed to determine if the disease-free interval and survival of patients who have squamous cell carcinoma of the head and neck, and who are at higher risk of relapsing, can be improved by adjuvant methotrexate following initial surgery, radiotherapy or both. The surgery and/or radiotherapy both are designed to create a situation where there is no clinically evident disease. This study will require at least 76 patients, who have relapsed in each of the treatment arms. Based on an annual accrual rate of 200 patients from the group, it would take approximately 28 months to complete.

263. LATE STAGE IV EPIDERMOID CARCINOMA OF THE ORAL CAVITY, LARYNX, AND HYPOPHARYNX

Niell, H. B., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee,* 38104, United States of America

This is a protocol investigating the use of radiotherapy and combination chemotherapy in patients with State IV epidermoid carcinoma of the oral pharynx, larynx and hypopharynx. This regimen will utilize the combination of methotrexate in fairly high dose, bleomycin, and cis-platinum, agents which are shown to be effective in the treatment of squamous cell carcinoma of the head and neck. This will be followed by 4000-5000 rads to the area, over 4-5 weeks. At the end of said treatment the possibility of surgery or follow-up care will be evaluated. It is, therefore, hoped that the results of this regimen will enable us to learn more about the ability of combination chemotherapy and radiotherapy to make patients who are initially inoperable, operable at a later date and, therefore, increase survival and cure.

264. CONCURRENT CHEMOTHERAPY - RADIOTHERAPY OF SELECTED CANCERS OF THE HEAD AND NECK - SOUTHWEST ONCOLOGY GROUP PROTOCOL 7863

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas,* 78284, United States of America

OBJECTIVES: To assess the local and systemic toxicity of the concurrent administration of the chemotherapeutic agents, bleomycin and hydroxyurea, with super voltage radiotherapy in treatment of locally advanced squamous cancer of the head and neck. To determine the maximum tolerated dose of both chemotherapy and radiotherapy when given according to the proposed regimen. A total of 18 have been entered onto this study. Fourteen patients are from the Audie Murphy VA Hospital and four of them have expired. A total of 39 patients have been entered from other institutions in the Southwest Oncology Group who are participating in this limited institutional pilot. The completed response rate is 48% and the plus partial response rate is 89%. Lack of response and survival show that a median response duration is 22 weeks and median survival 57 weeks.

265. A PROTOCOL FOR THE TREATMENT OF ADVANCED INOPERABLE CARCINOMA OF THE HEAD AND NECK

Spaulding, M., Lore, J., Sanani, S., Dayem, H., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Medical Oncology Section, *3495 Bailey Ave., Buffalo, New York,* 14215, United States of America

Two patients have been treated with a protocol entitled Treatment of Advanced Unresectable Carcinoma of the Head and Neck. This project is designed to investigate the use of simultaneous chemotherapy with irradiation in patients who have advanced unresectable tumors. The two patients have tolerated the treatment well although there has been severe mucositis. The mucositis was expected and was tolerated by the patients. It is too early to tell whether the hypothesis, i.e. that control of unresectable disease will be improved by the simultaneous administration of chemotherapy and radiation, will be proven.

266. ADJUVANT CHEMOTHERAPY (VCA) AFTER RADIOTHERAPY IN NASOPHARYNGEAL CARCINOMA

Molinari, R., Felci, U., Istituto Nazionale per lo Studio e la Cura dei Tumori, Dept. of Clin. Oncology C, *1 Via G Venezian, 20133 Milan, Italy*

The project aims to verify the effectiveness of an adjuvant long-term polychemotherapy treatment (VCR plus ADM plus CTX) after radical radiotherapy in nasopharyngeal carcinoma. All patients with histologically proven NPC in local-regional phase (except T1N0 and TxNxM1) receive full dose radical teleradiotherapy (60-70 Gy) (60Co, Line Ac., electron beam) including nasopharynx, base of skull, neck lymph nodes in both sides (including supraclavicular nodes). Six weeks after the end of RT patients with complete regression of T and N are randomized between no further treatment and adjuvant chemotherapy (VCR 1.2 mg/m2 i.v. (day 1) plus CTX 200 mg/m2/day (days through 4), per course). A course of CT is given every 4 weeks during 12 months. Patients with complete regression of T and PR and N are treated with radical neck dissection before randomization. Survival and length of disease-free interval will be the criteria for evaluation. The trial is multicentric, with 21 Cooperative Centers in Italy. Protocol and forms are also made for hospital-based registry of NPC in this country. An epidemiological form will be also available in a short time. The trial was activated Dec. 3, 1979. Fifteen cases have been included (Dec. 31, 1979).

267. ADJUVANT CHEMOTHERAPY IN TREATMENT OF HEAD AND NECK CARCINOMA

Schaefer, S. D., Middleton, R., Frenkel, E., Sudderth, J., Sheehan, R., Graham, M., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Division of Otolaryngology, *4500 S. Lancaster Rd., Dallas, Texas,* 75216, United States of America

Patients with advanced resectable head and neck carcinoma will be randomized into two treatment groups. Arm I of the protocol will consist of cis-diamminechloroplatinum (100 mg/M2 over 16 hrs. followed by an additional 24 hrs. of vigorously administered intravenous fluids) followed 21 days later by surgery and full course irradintion at 4-6 weeks postoperatively. These patients receive only one course of cis-diamminedichloroplatinum. Arm II is identical to the first arm of the protocol, except that these patients have not received chemotherapy. The goal of this study has been to assess the five year survival in the two groups. The investigators seek a positive correlation between adjuvant chemotherapy and increased five year survival.

At this time, 20 patients have been entered into the protocol. Seven of these patients have been randomized into Arm II, with the remaining 13 patients having received chemotherapy, surgery and irradiation. One patient has died in each of the treatment groups. It is too early for any assessments or judgments to be made regarding the success of chemotherapy in treatment of head and neck carcinoma at this time.

268. ADJUVANT CHEMOTHERPY, RADIOTHERAPY AND SURGERY VS. RADIOTHERAPY AND SURGERY FOR PREVIOUSLY UNTREATED HEAD AND NECK CANCER (ABBREV)

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas,* 78284, United States of America

Patients who have had no prior therapy and have histologically confirmed squamous cell carcinoma of the head and neck are eligible for this study. All patients must have a nonresectable lesion with no evidence of distant metastases. Patients must have a life expectancy of six weeks or greater and a good performence status with a BUN less than 20 mg% and a creatinine less 1.5 mg%. Patients must be seen by a surgeon, a radiotherapist and a medical oncologist prior to starting therapy.

The objectives are to compare the survival rates of Stage III and IV squamous cell carcinomas of the tongue, oral cavity, tonsil, oropharynx, hyporpharynx and larynx subjected to radiation therapy followed by surgical excision if possible, and then compare those rates to the survival rates of patients subjected to chemotherapy with cis-platinum, Oncovin and bleomycin followed by radiation therapy and surgical excision if possible, the latter rates in turn compared to the survival rates of patients subjected to chemotherapy with cis-platinum, Oncovin and bleomycin followed by radiation therapy and surgical excision if possible.

269. ADJUVANT CHEMOTHERAPY IN HEAD AND NECK SQUAMOUS CANCER

Taylor, S. G., Southwick, H. W., Caldarelli, D. D., Murthy, A. K., Rush University, School of Medicine, Dept. of Internal Medicine, *1725 W. Harrison St., Chicago, Illinois,* 60612, United States of America

A randomized study is proposed comparing no adjuvant chemotherapy with adjuvant chemotherapy in patients with stage II to IV squamous cell carcinoma of the upper aerodigestive systems, who are undergoing surgery and/or radiation therapy with curative intent. Chemotherapy consists of a 2-week course of 3 cycles of methotrexate with leucovorin (Arch. Otolaryngology, 1978) prior to surgery and radiation plus 4 months of adriamycin and cis-platinum given every 3 weeks following surgery and radiation (Cancer Treat. Rep., 62:1211, 1978). Patients will be followed for disease free status, sites and patterns of recurrence, and second primary development.

D. IMMUNOTHERAPY

270. IMMUNOLOGICAL STUDIES ON CANCERS FREQUENTLY OCCURRING IN INDIA - ORAL CANCERS

Gangal, S. G., Nair, P. N., Rao R. S., Cancer Research Inst., Biology Division, *Dr. Ernest Borges Marg, c/o Tata Memorial Ctr., Bombay 400012, Maharashtra, India*

OBJECTIVE: In our earlier studies we reported that oral cancer patients show cellular sensitization to autochthonous tumor extracts. The antitumor response can be maintained for 3-4 weeks in patients treated with surgery by intradermal inoculation of small doses of antigen. Experiments to increase antitumor immunity further, by inoculating patients with cauterized tumor antigen and BCG, have been undertaken.

APPROACH AND PROGRESS: Ten oral cancer patients treated with surgery received 5 mg of tumor antigen and 1 mg of BCG 2 days after operation and every 3 months thereafter. Control group was inoculated with BCG alone. Patients followed up for a year showed presence of tumor associated reactivity only in the group inoculated with BCG and tumor antigen. Marginal and temporary serum blocking activity could be demonstrated. At the end of one year, 3 patients from the experimental group remained tumor free and showed elevated antitumor immunity.

271. IMMUNO-STIMULANTS IN LOCALIZED RADIATION THERAPY

Wara, W. M., University of California, San Francisco Campus, School of Medicine, Dept. of Radiation Oncology, *551 Parnassus Ave., San Francisco, California,* 94122, United States of America

GOAL: To document the immunosuppression which occurs following radiation therapy to determine if a therapeutic advantage can be achieved by the addition of immunotherapy (thymosin) to the conventional treatment given for squamous cell carcinoma of the head and neck region and esophagus.

APPROACH: Both groups of head and neck and esophageal cancer patients will receive radiation therapy and/or surgery as treatment. Patients will then be randomized to receive thymosin or placebo in addition to standard treatment. All patients will be monitored with immunologic tests to measure antibody-mediated and cell-mediated immunity at regular intervals. The data will be analyzed for local disease recurrence, metastatic disease, and survival difference in the treatment groups.

272. LEVAM AS THERAPEUTIC ADJUNCT IN SQUAMOUS CARCINOMA

Strong, E. W., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York,* 10021, United States of America

The overall goal of this study is to improve the recurrence and survival rates of patients with epidermoid cancer of the head and neck by use of an immunopotentiator. A second major goal is to investigate immune reactivity in these patients and to correlate this with stage and site of disease, and with the clinical progress of the disease.

273. IMMUNOCHEMOTHERAPY WITH MTX AND CORYNEBACTERIUM PARVUM FOR HEAD AND NECK CARCINOMA FOLLOWING SURGERY AND RADIOTHERAPY

Oliveira Filho, J. A., Mestre, M., Centro de Estudos e Pesquisas Oncologicas de Campinas, Dept. de Oncologia Clinica, *Rua Alberto de Salvo, 311, Barao Geraldo, Campinas 13100, Sao Paulo Brazil*

OBJECTIVE: Determine both the toxicity and the degree of antitumoral activity of immunochemotherapy with MTX and C. parvum for head and neck carcinoma following surgery and radiotherapy.

PROTOCOL OUTLINE: Non-randomized study.

APPROACH: Arm I: MTX plus C. parvum.

DOSAGE SCHEDULE: Methotrexate 40 mg/m2 I.V., days 1 and 15, or 3 mg/m2 P.O. days 1-5. C. parvum 4 mg/m2 I.M. days 7 and 21. Dosage modification for toxicity will be given.

SPECIAL STUDY PARAMETERS: Skin tests.

END POINTS: Complete and partial response rates, duration of response, objective tumor response, toxicity/morbidity of treatment, survival time, survival rate.

CURRENT STATUS: Active since October 1978.

274. INTRATUMORAL IMMUNOTHERAPY PRIOR TO SURGERY

Neifeld, J. P., Lawrence, W., Blievernicht, S., Kaplan, A. M., Virginia Commonwealth University, Medical College of Virginia, Dept. of Surgery, *1200 E. Broad St., Richmond, Virginia,* 23298, United States of America

This protocol should determine whether or not presurgical intralesional treatment with C. parvum in conjunction with post-surgical C. parvum as an adjuvant to surgery in the treatment of epidermoid carcinoma of the head and neck will 1) decrease the incidence of a) local recurrence and b) distant metastases, 2) prolong the disease-free interval, and 3) increase the overall cure rate of the tumor. The experiments carried out in conjunction with this protocol will provide information on the prognostic value of monocyte chemotaxis in epidermoid carcinoma of the oral cavity, pharynx, and larynx. Moreover, these experiments should help elucidate some of the effects of C. parvum on monocyte function and antitumor effector function in man.

BIBLIOGRAPHIC REFERENCES: Pre-surgical Intratumor Immunotherapy of Carcinoma of the Head and Neck. G. Schuller, C. Squires, C.H. Moy, P. Brown, J. David Beatty, J.J. Terz, and A. Kaplan. Medical College of Virginia. Proc. Am. Assoc. of Cancer Research 19:223, 1978. Adjuvant Intralesional and Systemic Corynebacterium Parvum Immunotherapy for Surgically Treated Head and Neck Cancer. J. David Beatty, J.J. Terz, P. Brown, W. Lawrence, G. Schuller, and A. Kaplan. Surgical Forum 29:155-157, 1978.

275. TRANSFER FACTOR FROM INDIVIDUALS RECOVERED FROM INFECTIOUS MONONUCLEOSIS AS AN ADJUVANT IN RADIOTHERAPY OF NASOPHARYNGEAL CARCINOMA

Ho, J. H., Goldenberg, G., Chau, J. C., Kwan, H. C., Queen Elizabeth Hospital, *Kowloon, Hong Kong*

OBJECTIVE: To test the effectiveness of the transfer factor as an adjuvant in the radiotherapy of NPC patients with cranial nerve or base of skull involvement with or without cervical nodal involvement above the supraclavicular fossae. The transfer factor and placebo are prepared by the Manitoba Institute of Cell Biology and shipped to the Institute of Radiology without label so that the trial will be double-blind.

276. ADJUVANT IMMUNOTHERAPY IN THE TREATMENT OF PATIENTS WITH HIGH RISK MALIGNANT MELANOMA OF THE HEAD AND NECK, AND OF THE EXTREMITIES

Papac, R. J., Ariyan, S., Mitchell, M. S., Stansel, H. C., Glickman, M., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology/Oncology Service, *W. Spring St., West Haven, Connecticut,* 06516, United States of America

The aim of this study is to determine whether immunocompetence of melanoma patients at the time of diagnosis is of predictive prognostic importance, and whether immunostimulation with direct stimulation of draining nodes as well as by adjuvant immunotherapy will improve survival or disease free interval in malignant melanoma. The proposed study will include patients with head and neck melanomas, allocated on a random basis to receive monthly MER, intraoperative MER or both in addition to surgical intervention in a control surgical group. Cases of extremity melanomas also will be studied on a random basis to receive excision with perfusion of DTIC, and MER as well monthly, or intraoperative MER or both. The nodular and the spreading forms of melanomas will be segregated in the study.

Immunologic testing is to include in vitro testing of patients' lymphocytes against melanoma cells in culture, as well as skin testing.

277. CANCER CHEMOTHERAPY OF HEMATOLOGIC MALIGNANCIES

Saiers, J. H., Saiki, J., Hardy, W. R., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology & Oncology Section, *2100 Ridgecrest Dr. S.E., Albuquerque, New Mexico*, 87108, United States of America

PURPOSE: To evaluate chemotherapy and chemo-immunotherapy regimens in the treatment of human malignancies.

MATERIALS AND METHODS: Patients were treated according to tumor type on various protocols of the Southwest Oncology Group. Currently, there are 42 active protocols being used at this institution. In the past year, 22 patients have been registered on protocols.

RESULT: Four patients with malignant lymphomas were treated. Three achieved complete response and remain in complete remission. One achieved a partial response and has since relapsed. Two patients with malignant melanoma were treated. One had a complete response, but then refused further therapy until he had recurrence of his disease. Three patients suffering from malignancies of the bladder (1), salivary gland (1), lung (1) were treated and all achieved partial responses. One patient each with acute leukemia, malignancy of prostate, head and neck malignancy were treated and had no responses. A number of patients have been treated on Phase II studies including 4 lung, 2 melanoma, 1 each myeloma and lymphoma colon, and acute leukemia and none of these patients have responded to therapy. There has been no untoward toxicity during the past 12 months in any of our patients and we will continue to place as many patients on protocol as possible.

278. EFFECTS OF RADIATION THERAPY ON CELLULAR AND HUMORAL IMMUNITY OF PATIENTS WITH HEAD AND NECK CANCER (ABBREV)

Eells, R., McLaren, J., Olkowski, Z., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Radiology Service, *1670 Clairmont Rd., Decatur, Georgia*, 30033, United States of America

Accession of new patients has been closed, with 62 evaluable cases. The group randomized to adjuvant BCG/levamisole and the group receiving radiotherapy alone were reasonably comparable as to age, sex, site and stage. At entry, 64% showed impaired immunocompetence (as compared to age-matched controls without cancer). To date, there have been no significant differences between the immunotherapy and radiation only groups with respect to tumor control, disease-free interval, or survival curves. There were some variations between the two groups in the immunologic parameters, but these were not statistically significant. In vitro test results for all patients were as follows: T cell absolute numbers decreased at entry, with further fall at end of radiation, but recovery occurring at 8 weeks; T cell percentages decreased at entry, with no further changes after radiation or during follow-up to 40 weeks; B cell absolute numbers decreased at end of radiation, but with subsequent recovery maintained through 40 weeks; B cell percentages showed no significant alterations; blastogenesis (with PHA and PWM) decreased at entry, with further fall after radiation, and partial recovery during follow-up through 28 weeks; sialic acid levels elevated, with slight further rise at end of the radiation and gradual decrease toward normal at later follow-up. Lymphocyte cytotoxicity showed no apparent radiation effects, but has been discontinued because of complexity and variability of the results. Median survival had not been reached at last review. Monitoring of patients continues with periodic immunologic profiles. Further correlation of test results with clinical course and outcome with be made.

E. OTHER THERAPY MODALITIES

279. PROTOCOL ON TREATMENT OF CANCERS OF THE LIPS, ORAL CAVITY AND ONE THIRD OF THE TONGUE

Badellino, F., Fazio, M., Vercellino, V., Sannazzari, G. L., Istituto di Oncologia, *Via Cavour 31, 10123 Torino, Italy*

OBJECTIVE and APPROACH: T2. Treatment of cancers of the lips, oral cavity and 1/3 of the tongue.

PROGRESS: (See Minerva Stomatologica 27, 1,7-14, 1978). On March 31st, 1978, 683 patients were controlled and over 228 patients treated with radiotherapy, chemotherapy and surgery. Subsequently some other patients will have to be added (the number will be specified later).

Another group of patients has been treated with cryotherapy (plus possible radiotherapy or surgery).

280. PROTOCOL OF TREATMENT FOR RETINOBLASTOMA USING SURGERY, RADIOTHERAPY AND CHEMOTHERAPY - PHASE III

Lobo, J. F., Guerrero, L. J., Piza, E. J., Camacho, M. A., Hospital Nacional de Ninos, *Apdo. 1654, San Jose, Costa Rica*

OBJECTIVE: To establish the usefulness of treatment comprised of surgery, radiotherapy and chemotherapy according to stage of tumor.

APPROACH: Determination of stage: Stage 1 - surgery; Stage 2 -chemotherapy for 1 year (vincristine plus cyclophosphamide), surgery; Stage 3 - surgery, radiotherapy and chemotherapy using vincristine, cyclophosphamide, methotrexate; Stage 4 - same as 3 plus radiotherapy to metastases. Controlled trial.

PROGRESS: Twenty-five patients under evaluation. (Translated)

281. SWOG 8006 - PRE-OPERATIVE REDUCTIVE CHEMOTHERAPY FOR STAGE III-IV OPERABLE EPIDERMOID CARCINOMA (ABBREV)

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

Patients with operable stage III and IV epidermoid carcinoma of the oral cavity, oropharynx, hypopharynx and larynx without prior treatment are eligible for the study. All patients must have histologically confirmed diagnosis of squamous cell carcinoma and must have measurable lesions. All patients must have a resectable lesion, which is defined as that which can be resected according to basic surgical oncologic principles. The ultimate decision of operability rests on the expertise of the oncologic surgeon. Patients must be seen by the head and neck surgeon, radiation oncologist, and medical oncologist prior to initiation of study.

The objective is to determine the length of remission, recurrence rates, survival rates, and pattern of recurrence, for patients receiving therapy utilizing surgery and post-operative radiation versus combined therapies utilizing pre-operative chemotherapy, surgery and post-operative radiation therapy in operable stage III or IV epidermoid carcinoma of the head and neck.

282. ADJUVANT CHEMOTHERAPY IN OPERABLE HEAD AND NECK SQUAMOUS CARCINOMAS

Strong, M. S., Hong, W. K., Shapshay, S. M., Vaughan, C. W., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Dept. of Otolaryngology, *150 S. Huntington Ave., Boston, Massachusetts*, 02130, United States of America

OBJECTIVES: To compare in patients with operable squamous cell carcinoma of the oral cavity, oropharynx, larynx and hypopharynx the relative efficacies of (a) 'standard' therapy with surgery and postoperative radiation therapy, (b) 'standard' therapy plus preoperative induction chemotherapy with cis-Platinum/bleomycin, and (c) 'standard' therapy preceded by induction chemotherapy and followed by maintenance chemotherapy. Relative efficacies will be determined with respect to: incidence of local, regional and distant recurrence; total length of the disease-free interval; and survival. To compare the relative toxicities of the three regimens with particular attention to nutritional and performance status of the patient. To determine quantity and quality of tumor response prior to definitive local therapy.

This project is now in its second year.

283. STUDIES OF PATIENTS WITH DISSEMINATED SOLID TUMORS

Canellos, G. P., Sidney Farber Cancer Center Inc., *44 Binney St., Boston, Massachusetts*, 02115, United States of America

Independently and not as an agent of the Government, the Contractor shall exert its best efforts to conduct Phase II and Phase III Studies in Patients with Disseminated Solid Tumors. The tumors to be included in these studies shall be limited to the following: Large bowel cancer, bronchogenic cancer, malignant lymphoma, head and neck cancer, endometrial cancer, ovarian cancer, bladder cancer, soft tissue cancer, breast cancer, prostate cancer, bone sarcoma. A minimum of 400 patients shall be included in these studies with no fewer than 25 patients from any one tumor type group.

284. STUDIES OF PATIENTS WITH SOLID DISSEMINATED TUMORS

Burchenal, J. H., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

Independently and not as an agent of the Government, the Contractor shall exert its best efforts to conduct Phase II and Phase III studies in patients with solid disseminated tumors. The tumors to be included in these studies shall be limited to the following; lung carcinoma; ovarian carcinoma; cervical carcinoma; head and neck cacinoma; prostatic carcinoma; bladder carcinoma; and melanomas and sarcomas of soft tissue. A minimum of 400 patients shall be included in these studies with no fewer than 25 patients from any one tumor type group. All patients shall be treated intensively with chemotherapy either alone or in combination with other drugs, radiotherapy, immunotherapy or surgery in protocols to be agreed upon by the Project Officer and Principal Investigator. Protocols will include Phase II testing of new investigational drugs, Phase II testing of standard antitumor drugs not previously tested against the particular tumor type, and Phase III trials to determine the definitive activity of the above regimens.

285. NEW DRUG DEVELOPMENT CLINICAL TRIALS IN SOLID TUMORS

Golbey, R. B., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

OBJECTIVE: Furnish all necessary personnel, labor, patients, facilities, equipment, materials, and supplies required to conduct Phase II and Phase III studies in patients with disseminated solid tumors such as cancers of the lung, breast, prostate, bladder, kidney, testicle, ovary, endometrium, cervix, head and neck, stomach, pancreas, and colon, as well as lymphomas, melanomas, and bone and soft tissue sarcomas. Seventy-five patients are required for the first four month period, with 250 patients per year for the next four years. The final year of the contract is for patient treatment and follow-up only. Patients to be studied, accrued, and treated for each tumor type to be dictated by the particular protocols approved.

286. STAGE III AND IV EPIDERMOID CARCINOMA OF ORAL CAVITY, HYPOPHARYNX, AND LARYNX

Niell, H. B., U.S. Veterans' Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee*, 38104, United States of America

This protocol is to be used in Stage II and IV epidermoid carcinoma of the oral cavity, tongue, floor of the mouth, retrimolar trigone and lower alveolar ridge of the hypopharnyx and larynx. This study is aimed at differentiating whether standard therapy of surgery, followed by radiotherapy, can be improved upon by adding 3 active chemotherapeutic agents, i.e., methotrexate, bleomycin, and cis-platinum, for several courses prior to surgery and then at following these patients post-operatively. Patients will then be randomized between two arms: The first arm will include a 3 drug combination for two courses and then surgery; patients will be followed for relapse if metastatic disease or unresectable disease is found. The patients will have radiotherapy if no evidence of metastatic disease is found or the margins are free. The second arm of the randomization will include surgery and if the margins are free with no evidence of metastatic disease, the patients will receive radiotherapy over a 5 to 7 week course. We hope that by using this protocol we will be able to recognize the possible advantage of limited micro metastasis with chemotherapy prior to surgery and to determine whether this will add to prolongation of remission or, in fact, increase the cure rate.

287. PHASE II-III THERAPY IN ADVANCED HEAD AND NECK CARCINOMA (HUMAN)

Greenwald, E. S., Montefiore Hospital & Medical Center, *111 E. 210th St., Bronx, New York*, 10467, United States of America

This is part of a broader project. A summary of this subproject is not available.

VI. REHABILITATION AND PSYCHOLOGICAL ASPECTS OF TREATMENT

A. RECONSTRUCTIVE SURGERY AND PROSTHESIS DEVELOPMENT

288. EVALUATION OF REHABILITATION OF OROPHARYNGEAL CANCER

Logemann, J. A., Bytell, D. E., Northwestern University, Chicago Campus, School of Medicine, Dept. of Otolaryngology & Maxillofacial Surgery, *303 E. Chicago Ave., Chicago, Illinois*, 60611, United States of America

This study is designed to: 1) Evaluate the effects of ablation surgery of the oral cavity and oropharynx and associated reconstructive surgery on the psychological, communicative, and nutritional rehabilitation of patients with cancers of these areas; 2) assess the effectiveness of speech and swallowing rehabilitation in improving communication and deglutition; and 3) define the most effective rehabilitation techniques used to increase the patient's speech and swallowing function. Ninety patients with oral cancer requiring surgical treatment will be studied at five points in their protocol: 1) Before initiation of any treatment; 2) after radiation, if given (pre-or post-op); 3) after ablative surgery; 4) after the final surgical procedure to close any remaining fistulas or to reconstruct oral structures and before initiation of any rehabilitative intervention; 5) six months after initiation of oral feeding and speech and swallowing therapy. On each of these testing dates, each patient will complete a thorough examination protocol including detailed studies of: 1) Oral, pharyngeal, and esophageal function during deglutition; 2) oral and pharyngeal function during speech; 3) the source (neurologic) and extent of pain he experiences, if any; 4) his pattern and method of social communication; and 5) his psychosocial status. These evaluations will generate a profile of the patient's modal functioning at each point in his recovery. With the patient acting as his own control, the pre- and post-treatment profiles will be compared to provide an objective picture of the effects of the ablative surgery, surgical reconstruction, and speech and swallowing therapy on the patient's typical psychosocial and physiologic functioning.

289. REHABILITATION OF THE HEAD AND NECK CANCER PATIENT

Robson, M. C., University of Chicago, Pritzker School of Medicine, Dept. of Surgery, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

A multidisciplinary team approach for treatment and rapid rehabilitation of head and neck cancer patients is being evaluated. Rehabilitation begins as soon as the diagnosis is confirmed, rather than being delayed until treatment has been completed. New surgical and maxillofacial prosthodontic procedures are being evaluated to reconstruct head and neck defects using microvascular anastomoses for the transfer of soft and osseous tissue and alloplastic prostheses implanted by magnets or staples. This will allow the physical reconstruction time to be dramatically shortened and total psychosocial, dental, and speech rehabilitation to be completed more effectively.

290. MANDIBULAR RECONSTRUCTION WITH AUTOGENOUS MANDIBLE AND PERIOSTEAL GRAFT

Rice, D. H., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Head & Neck Surgery Section, *Wilshire & Sawtelle Blvds., Room 209, Los Angeles, California*, 90073, United States of America

This project is part of a larger study involving the regeneration of cartilage and bone from perichondrium and periosteum respectively in head and neck reconstruction. The first stage of mandibular reconstruction involved removing a short segment of mandible, autoclaving it, returning it to its original anatomic location, and covering it with a periosteal graft. The dogs were killed at varying times postoperatively and the area of the graft examined for new bone formation. This was assessed by both hematoxylin and eosin stains and by tetracycline fluorescence. New bone formation was found in relation to the periosteum in all dogs four weeks and older postoperative. Further studies will be done to assess the applicability of this technique to mandibular reconstruction in human head and neck cancer patients.

291. FUNCTIONAL LARYNGEAL AND TRACHEAL CONSTRUCTION POST-RESECTION

Rush, B. F., College of Medicine & Dentistry of New Jersey, New Jersey Medical School, School of Medicine, Dept. of Surgery, *100 Bergen St., Newark, New Jersey,* 07103, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

292. ELECTRONIC LARYNGEAL PROSTHESIS

Bailey, B. J., Leipzig, B., Everett, R. E., Young, K., University of Texas, Medical Branch at Galveston, School of Medicine, Dept. of Otolaryngology, *300 University Blvd., Galveston, Texas,* 77550, United States of America

The overall purpose of this project continues to be the development of an artificial voice source, fully encapsulated in a bio-compatible elastomer, for implantation in the neck after laryngectomy. Goals achieved during the current project year were: 1. Elimination of foreign body rejection reactions. This was achieved through use of a new encapsulant polymer and rounding of the transducer container contours. 2. Development of an experimental high-purity polyurethane elastomer for the bioencapsulant, and an outer porous surface to encourage fixation of the device in place. 3. Experiments with a high-purity rigid biocarbon device at the skin for signal and power transmission to the implanted transducer.

GOALS SET FOR THE COMING YEAR: 1. Simplification of the power and signal transmission system, using the biocarbon 'button'. 2. Refinement and testing of the polyurethane encapsulant. This will include histologic analysis of tissue reaction adjacent to the implanted material and monitoring of liver, spleen and local tissues. 3. Accelerated acoustic testing of prostheses while implanted in live and conscious animals. 4. At the end of the coming year, we plan to be prepared to begin investigation with implantation in human patients.

BIBLIOGRAPHIC REFERENCES: Young, K.A., Bailey, B.J., and Everett, R., Electronic Laryngeal Prosthesis for Implantation: A Progress Report II. Delivered before the 1979 American Speech and Hearing Association Convention, Atlanta, Georgia.

B. PSYCHOLOGICAL AND COMPREHENSIVE REHABILITATION

293. PSYCHOLOGICAL ASPECTS OF COLLUM CANCER

Gyllenskold, K., Tjernberg, B., Stockholms Universitet, Ped. Inst., Dept. of Educational Psychology, *10691 Stockholm, Sweden*

OBJECTIVE: To study psychological implications of collum cancer.

APPROACH: Interviews by psychologist.

PROGRESS: The study will start in October, 1980. Twenty-five patients will be interviewed on the following schedule: 1) At the time of diagnosis; 2) one week after this; 3) in the week following termination of treatments; 4) 6 months after time of diagnosis; 5) 12 months after time of diagnosis; 6) 18 months after time of diagnosis.

One close family member of each patient will be interviewed on the following schedule: 1) At the time of diagnosis; 2) 6 months after time of diagnosis; 3) 12 months after time of diagnosis; 4) 18 months after time of diagnosis.

294. PREPARATION OF PATIENTS FOR HEAD AND NECK SURGERY - EFFECTS OF REPEATED STIMULUS EXPOSURE

Finn, P., Clum, G. A., Chakravorty, R. C., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *Salem, Virginia,* 24153, United States of America

The purpose of this study is to assess the effect on the anxiety and depression levels of patients undergoing surgery for head and neck cancer of a consultant providing extra information by means of slides and discussion. All patients will be prepared for the surgery by the surgeon in his usual way. The randomly selected experimental subjects will be offered three visits by a consultant who can show them slides of previous people, before and after the same operation, and discuss the operation. Control subjects will receive three visits with only emotional support. All patients will be assessed as to their coping style by means of a structured interview and anxiety and depression levels will be followed during the course of the hospitalization. The hypothesis is that all patients will benefit from the extra attention of the experimenters, but that the information seekers among the experimental group will show the greatest improvement over the control group. If this proves to be the case, in the future we plan to offer different preparation for surgery, depending upon the patient's coping style.

This project has been suspended due to personnel loss. Not enough data has been collected to be analyzed at this time. We are unable to estimate when study will be resumed at this time, but data will be kept until we are able to use it.

295. EVALUATION OF REHABILITATION OF OROPHARYNGEAL CANCER

Logemann, J. A., Bytell, D. E., Northwestern University, Chicago Campus, School of Medicine, Dept. of Otolaryngology & Maxillofacial Surgery, *303 E. Chicago Ave., Chicago, Illinois,* 60611, United States of America

The summary for this project is under entry no. 288.

296. A PILOT STUDY OF THE NEED FOR AFTERCARE OF HEAD AND NECK CANCER PATIENTS

van den Heuvel, W. J., van Burink Withaar, A. G., RoodNieuwland, A., Studicentrum voor Soc. Oncologie, *Dr. Molewaterplein 50, Rotterdam, Netherlands*

OBJECTIVE: A pilot study: a) to determine the need for aftercare of head and neck cancer patients; b) to evaluate the information about patients given by the hospital to the district nurse; c) to evaluate the care patients received from the district nurse (patients' evaluation).

APPROACH: Forty patients treated for head and neck cancer in a university clinic and 32 district nurses are interviewed.

PROGRESS: Data collecting has been finished. The report on the pilot study will be completed in April 1979.

297. NUTRITIONAL REHABILITATION IN HEAD AND NECK CANCER

DeCosse, J. J., Memorial Hospital for Cancer & Allied Diseases, Dept. of Surgery, *1275 York Ave., New York, New York,* 10021, United States of America

The objective of the proposed randomized trial is to compare two methods of providing nutritional rehabilitation to patients with advanced head and neck cancer: intensive nasogastric tube feeding vs. optimal oral nutrition. The overall goal is to evaluate the effects of aggressive nutritional support on the patient's ability to tolerate and respond to radiation therapy and, in some cases, chemotherapy, as well as its effects on recurrence and survival.

Questions to be studied include differences in caloric and protein intake, weight, amount and duration of therapy, and severity of reactions to therapy; taste and smell impairment during therapy; the pattern of recovery of taste and smell following therapy and the effects of zinc therapy on this recovery; techniques for improving patient nutrition, both orally and extraorally; and the long-term consequences of aggressive nutritional support during short-term therapy.

Patients will be randomized into two groups: one will receive optimal oral nutrition and the other nasogastric feedings in addition to optimal oral nutrition. Both groups will receive support for an 11-week period. Thereafter, both groups will receive identical oral nutritional support for a two-year follow-up period.

Patients in both groups will also be randomized into groups receiving zinc therapy or a placebo to assess the role of zinc in the recovery of taste.

VII. TRAINING PROGRAMS FOR DENTAL PROFESSIONALS

298. TRAINING PROGRAMS FOR DENTAL TECHNICIANS

Chalian, V. A., Indiana University - Purdue University at Indianapolis, School of Dentistry, Dept. of Maxillofacial Prosthetics, *1121 W. Michigan St., Indianapolis, Indiana,* 46202, United States of America

OBJECTIVE: Develop, conduct, and evaluate training programs for maxillofacial prosthodontists and maxillofacial dental technicians.

299. TRAINING PROGRAMS FOR DENTAL TECHNICIANS

Schaaf, N. G., Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York,* 14263, United States of America

OBJECTIVE: Develop, conduct, and evaluate training programs for maxillofacial prosthodontists and maxillofacial dental technicians.

300. TRAINING PROGRAMS FOR DENTAL TECHNICIANS

Aramany, M. A., Eye & Ear Hospital of Pittsburgh, *230 Lothrop St., Pittsburgh, Pennsylvania,* 15213, United States of America

OBJECTIVE: Develop, conduct, and evaluate training programs for maxillofacial prosthodontists and maxillofacial dental technicians.

301. TRAINING PROGRAMS FOR DENTAL TECHNICIANS

Drane, J. B., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas,* 77030, United States of America

OBJECTIVE: Develop, conduct, and evaluate training programs for maxillofacial prosthodontists and maxillofacial dental technicians.

302. CLINICAL CANCER EDUCATION PROGRAM (DENTAL)

Martinez, M. G., Alling, C. C., Castleberry, D. J., Bodden, R. W., Durant, J. R., Brascho, D. J., Hoffman, S., University of Alabama in Birmingham, School of Medicine, Dept. of Pathology, *1919 7th Ave. S., Birmingham, Alabama,* 35233, United States of America

The main objective of this proposal is to develop and implement an educational program to provide a broad and advanced knowledge of oral cancer to undergraduate students of dentistry, to postgraduate and graduate students, to practicing dentists, to auxiliary health personnel and to the public so that the quality of health care can be improved with the final result of a lower mortality rate from oral cancer.

This could be accomplished through: (1) Undergraduate programs for dental students, dental hygienists and dental assistants above and beyond those provided in the regular curriculum of dental schools on oral cancer; (2) special education programs for graduate and postgraduate students with new concepts in early diagnosis and management of oral malignancies; (3) continuing education courses for practicing dentists, physicians and auxiliary personnel to improve the clinical skills in the detection, prevention and rehabilitation of patients with oral cancer and to stress the increasing responsibility of the dental profession in the multidisciplinary approach to the management of patients with complications following therapy for cancer of the oral and paraoral regions; and (4) educational programs for the general public in an attempt to make them aware of the importance of early detection in curability of oral cancer, as well as in prevention of oral lesions.

303. CLINICAL CANCER EDUCATION PROGRAM

Beumer, J., Christensen, R. E., Harrison, R., Herzberg, F., Sapp, J. P., Tupac, R., University of California, Los Angeles Campus, School of Dentistry, Dept. of Dentistry, *405 Hilgard Ave., Los Angeles, California,* 90024, United States of America

The purpose of this program is to increase the diagnostic and therapeutic skills of dental students, practicing dentists and associated paraprofessionals with regard to patients who have head and neck tumors. The educational program is oriented towards detection of head and neck neoplasms, maintenance of oral health and function at optimal levels throughout therapy, and rehabilitation of patients with disfiguring functional or emotional deficiencies secondary to treatment. Additionally, post-graduate education courses will be conducted for the local dental and medical community.

BIBLIOGRAPHIC REFERENCES: Beumer J., Curtis, T. and Harrison R.: Radiation Therapy of the Oral Cavity - Sequelae and Management, Part 1. Head and Neck Surgery, 1:301-312, 1979. Miller, L.W., Davis, R.M., Beumer, J., and Cullen, J.W.: Chapter 32, Physical Rehabilitation in Cancer Treatment: A Multidisciplinary Approach, ed. by C.M. Haskell. W.B. Saunders Co. (in press), 1980.

304. CLINICAL CANCER EDUCATION PROGRAM

Silverman, S., Zlotolow, I., Greenspan, D., Ordway, D., Ratner, V., University of California, San Francisco Campus, School of Dentistry, Dept. of Oral Medicine & Hospital Dentistry, *551 Parnassus Ave., San Francisco, California,* 94122, United States of America

Oral cancer accounts for approximately 5% of all cancers in the United States and is keeping pace with the relative yearly increase in cancer incidence. The overall 5-year survival in these malignancies is less than 40%. Therefore, public and professional awareness of early recognition and adequate management is essential.

The objective is to combine demonstration and education in a diversified multidisciplinary program of oral cancer control for undergraduate, graduate and postgraduate dental students and dentists, as well as medical and paramedical personnel. This will be accomplished through education in the following: early cancer detection and recognition of recurrence; prevention; methods of caring for dental and paradental tissues before, during and after therapy; rehabilitation through replacement of missing tissues by prostheses and psychosocial intervention.

305. CLINICAL CANCER EDUCATION PROGRAM

Greer, R. O., Ryan, D. E., Boone, M. E., Golitz, L. E., Huffner, W. E., Johnson, F. B., Robinson, W. A., Wood, R. P., Jafek, B. W., University of Colorado, Health Sciences Center, School of Dentistry, Dept. of Oral Biology, *4200 E. 9th Ave., Denver, Colorado,* 80220, United States of America

The objectives of the clinical cancer education program at the University of Colorado School of Dentistry are threefold. The first objective is to enhance the diagnostic acumen of dental students, dental general practice residents, practicing dentists, faculty and associate health professionals as it relates to the detection of neoplasia of the head and neck. A second goal is to increase the management and therapeutic competence of all of the aforementioned in the realm of head and neck neoplasia. The third objective is to reinforce the concept of a team approach to the prevention, diagnosis, treatment and rehabilitation of the head and neck cancer patient.

This narrative has been prepared in accordance with an October 16, 1978 NIH directive to better regulate the length of research grant applications.

306. CLINICAL CANCER EDUCATION (DENTAL)

Weathers, D. R., Waldron, C. A., Halstead, C. L., Budnick, S. D., Baumgarten, R. F., Crawford, B. E., Emory University, School of Dentistry, Dept. of Oral Pathology, *106 Forest Ave. N.E., Atlanta, Georgia,* 30303, United States of America

OBJECTIVES: This project seeks to improve and expand an ongoing cancer education program at Emory University School of Dentistry at the undergraduate, post-graduate and continuing education levels; develop a position of Clinical Associate in Oral Cancer at the post-residency level; develop two Clinical Assistantships in Oral Cancer at the undergraduate level; expand cancer education for dentists in the community and state and region; and continue to expand the diagnostic and consultative services of Emory University School of Dentistry at all levels of the program in an effort to improve oral cancer detection and management.

307. CLINICAL CANCER EDUCATION PROGRAM (DENTAL)

Drummond, J. F., Castich, E., Damm, D. D., Little, J. W., White, D. K. University of Kentucky, School of Dentistry, Dept. of Oral Pathology, *Limestone & Euclid, Lexington, Kentucky,* 40506, United States of America

The goal of this program is to provide more comprehensive knowledge of head and neck cancer to dental students, practicing dentists and other health professionals. This goal will be achieved through the introduction of new courses into the dental curriculum which concern head and neck cancer and through modification and expansion of the existing outreach program.

308. CLINICAL CANCER EDUCATION PROGRAM (DENTAL)

Burzynski, N. J., Miller, R. L. University of Louisville, School of Dentistry, Dept. of Oral Diagnosis & Oral Medicine, *129 E. Broadway, Louisville, Kentucky,* 40202, United States of America

The Clinical Cancer Education Program concerns itself with the instruction of undergraduates, graduates and auxiliaries in the current concepts of prevention, detection, diagnosis, treatment and rehabilitation of oral-facial cancer. Emphasis is placed on a multidisciplinary approach to cancer detection and care, with emphasis on head and neck cancer. Evaluation of various educational experiences in cancer related topics is applied to various facets of the program. Computer Assisted Self-Evaluation (CASE) programs, Symposia, and Continuing Education Courses on both the institutional and outreach levels are presented to the practitioners and auxiliaries. Clinical Cancer Assistantships are offered to interested and qualified individuals.

BIBLIOGRAPHIC REFERENCES: George, D.I., Burzynski, N.J., and Miller, R.L. Reactive Properties of Oral Lesions to the Specific Red Cell Adherence Test. Oral Surg. 47:51-57, 1979. Burzynski, N.J., Kupchella, C.E., Calhoon, T.C., and Reid, K.H. The CASE System for Cancer Education. J. of Dent. Education. April 1979, in press.

309. CLINICAL CANCER EDUCATION PROGRAM

Guerra, L. R., Legett, B. J., Kent, J., Boozer, C., Ellis, D. J., Quinn, J. H., Carr, R. F. Louisiana State University, Medical Center, School of Dentistry, Dept. of Oral Pathology, *1542 Tulane Ave., New Orleans, Louisiana,* 70112, United States of America

This program is intended to improve the status of patients with cancer through the education and training of health professionals and the general public. It provides classroom instruction; patient contact and clinical project experiences; readily available core audiovisual and reference materials; specialty training; continuing education; and public information, screening and biopsy services. It employs an array of separate but related activities directed toward dental students and auxiliaries, graduate students and practicing dentists, and the lay public. It includes both cognitive and affective learning related to the diagnosis, treatment, rehabilitation and maintenance of cancer patients. Both intramural and extramural sites are used.

310. CLINICAL CANCER EDUCATION PROGRAM - ORAL ONCOLOGY

Goldman, H. M., Feldman, M. I., Richardson, J., Mozden, P. J., Strong, M. S., Boston University, School of Dentistry, Dept. of Oral Pathology, *755 Commonwealth Ave., Boston, Massachusetts,* 02215, United States of America

The Clinical Cancer Education Program (CCEP) in the School of Dentistry has developed and now evaluated a series of educational activities as presented in the grant application. At the outset of the grant, it is noted that the intent of the proposed work was to provide dental students and practitioners with more training and education in oncology, particularly to produce enough intellectual and psychological insight in the current multidisciplinary aspects of cancer management so that the general practicing or specialized dentist might feel both equipped and motivated to participate in the management team. This work has now been conducted for 2 years at the dental school permitting a didactic lecture program in oral oncology as well as general oncology for the third year dental students, and oncology lecture program for the fourth year dental students as well as the post-graduate specialists in periodontics. In addition, small teams of third year students have visited the Department of Radiation Medicine for actual patient contact and the observation of the clinical practice of multidisciplinary oral cancer management. A faculty of medical, surgical, radiation, and head and neck oncologists as well as specialists in voice rehabilitation, maxillofacial prosthesis, pathology and other allied health professionals have been recruited to this effort. In the coming year, it is now planned to extend the educational program to the dental assistants and hygienists, and the practicing dentist by seminars at the district dental society meetings, and to evaluate in a more sophisticated fashion the cognitive and attitudinal changes accomplished through the educational interventions.

311. CLINICAL CANCER EDUCATION PROGRAM

Shklar, G., Sonis, S. T., Atwood, D., Guralnick, W., Hargreaves, A., Salt, D., Harvard University, Boston Campus, Harvard School of Dental Medicine, Dept. of Oral Medicine & Oral Pathology, *188 Longwood Ave., Boston, Massachusetts,* 02115, United States of America

OBJECTIVE: A comprehensive and multidisciplinary program of education in clinical oral cancer aimed at improving the early diagnosis, treatment and overall care of the patient with oral cancer, as well as the oral care of all cancer patients, particularly those undergoing active therapy. The program will involve undergraduate dental students; graduate dental students; dentists, physicians, dental hygienists, dental assistants, visiting nurses, public health nurses and other health personnel in the community; medical students, interns and residents in the various Harvard affiliated hospitals. Subject matter will deal with all phases of the oral cancer treatment ranging from prevention through screening, diagnosis, therapy, up to rehabilitation. The teaching of oral and dental care for all cancer patients will be developed and presented to undergraduate and graduate dental students as well as to dentists and auxiliary dental personnel in the community, with clinical experience in the setting of a Comprehensive Cancer Center as well as in other appropriate facilities. A major part of the program will be the continued development of graduate education in oral oncology, with three clinical associates per year receiving training and experience in all phases of oral cancer management, providing an opportunity for developing comprehensive skills in a specialized field of oral oncology such as maxillofacial prosthetics.

312. CLINICAL CANCER EDUCATION PROGRAM

Cataldo, E. F., Tufts University, Boston Campus, School of Dental Medicine, Dept. of Oral Pathology, *136 Harrison Ave., Boston, Massachusetts,* 02111, United States of America

An integrated preclinical and clinical cancer education program for all undergraduate dental students is proposed utilizing combined resources of Tufts University School of Dental Medicine, Tufts University School of Medicine and the New England Medical Center Hospitals. The objectives of the program are directed to preparing the dental student to: Better understand and appreciate the nature of cancer problems and principles of their management in order to enable them to practice better dentistry; develop improved skills in the diagnosis and management of oral cancer; develop the ability to recognize or suspect certain cancer problems which may come to their attention and to appreciate the need for and technique of referring patients with such problems to physician colleagues.

The overall educational program may be summarized as: 1. Preclinical dental science of oral oncology: a. Introduction to oral oncology. b. Oral pathology of cancer. c. Oral oncology lectures. 2. Introduction to clinical medicine: a. Physical diagnosis: History and physical exam. b. Medical lectures: General pathology, oral pathology, oral medicine, head and neck cancer, laboratory medicine, clinical pharmacology. 3. Clinical medicine: a. Medical lectures (ear, nose and throat, common malignancies, chemotherapy, radiotherapy). b. Hospital clerkship (medical oncology, radiotherapy, otolaryngology).

313. CLINICAL CANCER EDUCATION PROGRAM

Gier, R. E., Barker, B., Feil, P., University of Missouri, Kansas City Campus, School of Dentistry, Dept. of Oral Diagnosis, *10th & Troost Sts., Kansas City, Missouri,* 64110, United States of America

This project will design and implement (a) a multidisciplinary education program in head and neck cancer for the undergraduate dental student and dental hygiene student; (b) a continuing education program for dental practitioners, dental auxiliaries, physicians, nurse practitioners; and (c) a public education program.

The program will provide multidisciplinary classroom and clinical instruction to dental students in (a) the detection and diagnosis of head and neck cancer, (b) the dental evaluation and complementary dental treatment of the patient, (c) treatment modes, (d) psychosocial aspects of the dentist-patient relationship, (e) nutritional problems of the cancer patient. Students will be involved in simulated case studies, and case presentations. Dental students will receive beginning-to-end clinical experience with head and neck cancer patients and extensive clinical experience with cancer patients referred from hospitals in a four county area. Students will also participate in tumor boards and make use of a tumor registry.

The hygiene program will include some classroom instruction in such areas as detection, complementary dental treatment, nutrition, psychological needs and reactions of the cancer patient. Hygiene students will also participate in the head and neck cancer clinic.

A series of continuing education programs will be developed for health professionals involved in the diagnosis and treatment of head and neck cancer. Each program will be composed of a formal presentation and a workshop. A series of clinical pathology conferences will also be organized.

314. CLINICAL CANCER EDUCATION PROGRAM

El Mofty, S. K., Washington University, School of Dental Medicine, Dept. of Biomedical Science, *4559 Scott Ave., St. Louis, Missouri*, 63130, United States of America

Washington University School of Dental Medicine proposes a Clinical Cancer Education Program which will coordinate and improve the teaching about neoplasia at the undergraduate, postgraduate and continuing education levels. Fundamentally this program will be a continuation and expansion of a previous program. At the undergraduate dental student level the following changes are proposed: 1) To improve, revise, and enlarge the self-teaching program in pathology, 2) to continue the autopsy and Radiation Oncology Screening Program rotations, 3) to enlarge the Oral Oncology course for senior dental students from sixteen to eighteen hours, 4) to create an eighteen hour course on dental radiology and 5) to continue the senior biopsy requirement. At the postgraduate level we propose to: 1) Enlarge the Advanced Oral Pathology course from eighteen to thirty-six hours with a great majority of this time devoted to the recognition of oral lesions and 2) to encourage the attendance and participation of the postgraduate students in the Oral Oncology course. At the continuing dental education level we propose to offer an all-day symposium on head and neck cancer for the dental profession (all of the dental profession, not just dentists) and to make this program available to our undergraduates and postgraduates at no cost.

315. CLINICAL CANCER EDUCATION PROGRAM - DENTAL

Greene, G. W., Natiella, J. R., Meenaghan, M. A., Schaaf, N. G., Pickren, J. W., Shedd, D. P., State University of New York, Health Science Center at Buffalo, School of Dentistry, Dept. of Oral Pathology, *3435 Main St., Buffalo, New York*, 14214, United States of America

The Cancer education program has coordinated and produced a comprehensive core curriculum with several special programs designed to broaden the scope of the present curriculum. Our review of cancer education in various disciplines, e.g., oral pathology, oral surgery, oral medicine, prosthetics and comprehensive dental care indicates we have structured a program which will benefit dental and medical students and residents, postdoctoral trainees, practicing dentists, physicians, nurses, dental hygienists and dental assistants. A program has been developed on cancer awareness with the local and regional dental and medical society members and a head and neck program has been presented. A hospital program for postdoctoral trainees specifically related to head and neck cancer has been implemented. A hospital program on autopsy and surgical pathology has been implemented for medical and dental pathology residents. A logbook has been instituted in our comprehensive care clinic and all unusual lesions are recorded and followed until a definitive diagnosis is made. All cases are seen on a consultative basis with at least one member of the Oral Pathology Department. This program has helped cancer education of our clinical dental faculty enormously. Our preventive dental clinic has developed an indoctrination and expansion of duties for dental hygienists and dental assistants. These programs were initially proposed and are presently in their early development. It is hoped that we will be able to give a realistic evaluation of its effectiveness in cancer education after three years of operation.

316. CLINICAL CANCER EDUCATION (DENTAL)

Lepley, J. B., Argerakis, G., Scannell, J. B., Strong, E., Stoll, J. B., Memorial Hospital for Cancer & Allied Diseases, Dental Service, *1275 York Ave., New York, New York*, 10021, United States of America

The objective of this program is to educate three Clinical Associates annually in an A.D.A. approved curriculum in maxillofacial prosthetics.

The Associates will receive both clinical and didactic training in all aspects of maxillofacial prosthetics, particularly those aspects relating to the treatment of patients with head and neck cancer. The education they receive at Memorial Hospital will be multidisciplinary and will include clinical involvement with such areas as radiotherapy, chemotherapy, surgery, rehabilitation, etc.

The Associates will also attend lectures and courses at the New York University College of Dentistry and the U.S. Naval Graduate School of Dentistry. These lectures and courses, combined with lectures and seminars to be attended at Memorial Hospital, will provide strong academic training in both maxillofacial prosthetics and cancer treatment.

The Associates will receive education and training that will enable them, upon graduation, to assume faculty and staff positions at dental schools, medical centers, and cancer centers. These individuals, when assuming such positions, will have the broad viewpoint of cancer patient management so vital to the multidisciplinary approach necessary for both teaching and clinical practice.

317. ORAL/HEAD AND NECK CLINICAL CANCER EDUCATION PROGRAM

Watkins, F. S., Young, S. K., University of Oklahoma, Health Sciences Center, School of Dentistry, Dept. of Continuing Dental Education, *Box 26901, Oklahoma City, Oklahoma*, 73190, United States of America

This project will design and implement additions for a multidisciplinary education program which addresses three major components of dental care in oral/head and neck cancer. The program consists of educational activities for dental health professionals and consumers which will provide sources of training, coordination and an information exchange for Oklahoma dental students, dental hygiene students and dental practitioners. The consumer education program will provide information on oral cancer and instruction on self-examination to persons identified as regular dental patients and to the public sector who may or may not seek regular dental care.

The professional educational program will be developed through symposia, workshops, development of audiovisual materials, and development of a patient referral information system. Further educational experiences will be provided through a dental oncology unit which will provide opportunties for dental management of the oral/head and neck cancer patient.

A formative evaluation will be planned to address the need to determine what Oklahoma dentists know and don't know about oral/head and neck cancer, the problems of patient adherence to the self-examination technique, the effects of instruction on the number of oral/head and neck cancer patient referrals and the mechanism of the educational system being developed.

318. CLINICAL CANCER - DENTAL

Miller, A. S., Mohnac, A. M., Simpson, T., Ries, G., Harwick, R. D., Chen, S., Fantasia, J. E., Temple University, School of Dentistry, Dept. of Pathology, *3223 N. Broad St., Philadelphia, Pennsylvania*, 19122, United States of America

Temple University School of Dentistry proposes institution of a Clinical Cancer Education Program to coordinate, expand and augment cancer education at the undergraduate and postgraduate levels, as well as the dental hygiene and continuing education programs. Part of the program will be conducted at extramural locations, such as Temple University Hospital and American Oncologic Hospital, by the coordinator of hospital dentistry. This will provide hospital and tumor clinic exposure for dental students and dental hygiene students. We propose continuing a program of oral health care for patients undergoing radiation therapy for malignant oral, head and neck neoplasms, involving graduate students in periodontology and dental hygiene students. The general program objectives are to: (1) Provide undergraduate and postgraduate dental students and dental hygiene students with the basic principles of cancer biology, epidemiology, detection, diagnosis, treatment, prevention and control; (2) establish appropriate attitudes and motivation for continued education regarding cancer, which will carry over into the practice years; and (3) develop and foster concepts of cooperative humane care for the oral cancer patient, especially oral rehabilitative care. The overall administration of the Clinical Cancer Education program will be through the Department of Pathology in cooperation with the Cancer Education Committee and the Departments of Oral Surgery and Oral Diagnosis.

BIBLIOGRAPHIC REFERENCES: Goldstein, R.H., Byrne, J.E. and Miller, A.S.: Clinical-Pathological Conference - Chronic sclerosing osteomyelitis. J. Oral Surg. 37:52-53 and 37:101-102, 1979. Chen, S.-Y. and Miller, A.S.: Neurofibroma and Schwannoma of the oral cavity. A clinical and ultrastructural study. Oral Surg. 47:522-528, 1979.

319. CLINICAL CANCER EDUCATION GRANT

Pliskin, M. E., University of Pennsylvania, School of Dental Medicine, Dept. of Pathology, *4001 Spruce St., Philadelphia, Pennsylvania*, 19104, United States of America

The overall objectives of the Clinical Cancer Education Grant are to train and educate dental, graduate, postgraduate and dental hygiene students to become competent in the detection, diagnosis and management of head and neck cancer with specific emphasis on oral cancer. These objectives will be accomplished by developing a program which utilizes the following cancer educational mechanisms: 1. Surveillance. 2. Head and Neck Cancer Teams and Principles of Referral. 3. Routine Dental Care for Oncology. 4. Development of Individualized Treatment Plans for Oncology Patients' Home Care Regimen. 6. Follow-up for Oncology Patients. 7. Hospital Dentistry. 8. The Dentist's Role in Cancer Care.

320. CLINICAL CANCER EDUCATION GRANT

Verbin, R. S., Aramany, M. A., Myers, E., Zaki, H. S., Fischer, W., University of Pittsburgh, School of Dental Medicine, Dept. of Diagnostic Services, *C336 Salk Hall, Pittsburgh, Pennsylvania*, 15213, United States of America

It is the objective of this program to augment our basic cancer education curriculum with an integrated, readily identifiable, multidisciplinary didactic course coupled with expanded clinical experiences. The didactic component will be structured into a new block of curricular time which will represent a required course for the entire third year class of dental students. Additional clinical experiences will be provided via participation in the various activities of the Regional Center for Maxillofacial Prosthetic Rehabilitation. In this latter facility, the students will be engaged in: (1) The further development of skills in proper examination procedures; (2) teaching patients a routine that can be utilized for self-examination of the oral cavity; (3) pretherapeutic evaluation of new cancer patients; (4) management of irradiated patients; (5) management of patients on chemotherapeutic regimens; (6) operating room procedures; (7) providing dental care for oral cancer patients.

321. CLINICAL CANCER EDUCATION PROGRAM (DENTAL)

McCarty, G. A., Wells, J. E., Butts, H. C., Brown, D. M., Cipra, D., Coury, V. M., University of Tennessee, Center for the Health Sciences, School of Dentistry, Removable Prosthodontics & Maxillofacial Prosthetics Dept., *62 S. Dunlap St., Memphis, Tennessee*, 38103, United States of America

OBJECTIVES: To develop and maintain an active, coordinated approach to clinical cancer education for the dental community. To increase competence of the students in the oral cancer screening examination, biopsy, and cytology techniques and to promote their routine use in general practice. To provide increased clinical experience in the dental management and treatment of oral cancer. To provide the opportunity for the student to become proficient in the dental management of patients receiving radiotherapy and chemotherapy treatment for head and neck cancer. To provide increased opportunity for students to participate in maxillofacial prosthetic rehabilitation procedures for head and neck cancer patients. To provide continuing cancer education of both a clinical and a didactic nature for the dental practitioners of this geographical area.

322. CLINICAL CANCER EDUCATION PROGRAM (DENTAL)

Elzay, R. P., Virginia Commonwealth University, School of Dentistry, Dept. of Oral Pathology, *901 W. Franklin St., Richmond, Virginia*, 23284, United States of America

The purpose of the application is to obtain financial assistance to improve cancer education for dental students, dental hygiene students, postgraduate students, faculty and practitioners beyond the content of the existing cancer program in the dental school curriculum. The goals of the program will be: 1. To continue to improve and extend cancer education for undergraduates, postgraduates, dental hygienists, practicing dentists and faculty. 2. To make our dentists and patients aware of the existing informational material available through our Health-Line (Dial-A-Tape) Program and promote the use of these resources. 3. To implement a continuing educational oral cancer detection activity within the State of Virginia. 4. To continue an ongoing objective, orderly analysis and evaluation of the Oral Cancer Curriculum within the School of Dentistry. 5. To assist in the maintenance of the established Oral Tumor Registry, Computerized Oral Tumor Recall Program, and Recall and Referral Clinic as educational instruments at the undergraduate, graduate and postgraduate levels.

VIII. BROAD CLINICAL PROGRAMS

323. SOUTHEASTERN CANCER STUDY GROUP

Velez Garcia, E. O., University of Puerto Rico, Medical Sciences Campus, School of Medicine, Dept. of Medicine, *P.O. Box 5067, Rio Piedras*, 00936, Puerto Rico

We seek to participate actively in all the activities of the Southeastern Cancer Study Group. Our main goal is to continue, through this participation, clinical trials in the evaluation of chemotherapeutic agents in malignant disease. We are especially interested in conducting these trials in a multidisciplinary way with the inclusion of radiotherapists, clinicians, surgeons, pathologists, and basic scientists in the team. As in the case of the Southeastern Cancer Study Group, a major emphasis will be placed on thorough protocol implementation and review as well as quality control. Because of the high incidence of neoplasms of the head and neck in our environment we plan to develop new adjuvant approaches to these tumors. A pilot study utilizing chemotherapy and radiotherapy for advanced head and neck tumors has been completed.

Our goals are: (a) Continued interest in development of an integrated multimodal approach for the management of patients with breast cancer. Our protocol SEG No. 76BRE 0103 is now accruing patients at a relatively fast rate and we hope that it will help elucidate the possible role of radiotherapy and adjuvant chemotherapy in patients with positive axillary nodes. (b) Development of a combined chemotherapy-radiotherapy approach for patients with advanced (T-3 and T-4) head and neck cancer. Forty patients have been entered on such a study; partial results have been published. (c) Development of a four-drug regimen for treatment of refractory lymphomas.

324. CHILDREN'S CANCER STUDY GROUP

Heyn, R. M., Ertel, I., Hutchinson, R. J., Hanash, S., Holland, R., Heidelberger, K., Schnitzer, B., Waskerwitz, M., Hanson, T., University of Michigan, Ann Arbor Campus, Medical School, Dept. of Pediatrics & Communicable Diseases, *1335 E. Catherine St., Ann Arbor, Michigan*, 48104, United States of America

The Children's Cancer Study Group is engaged in carrying out clinical research studies which have been developed by senior investigators in the group and approved by the NCI. These programs, which are designed to improve the care and survival of children with leukemia and solid tumors, include both Phase II and Phase III studies. Phase II studies are primarily those involving new agents which have completed Phase I trial.

The current study for children with newly diagnosed acute lymphocytic leukemia involves stratification at diagnosis based on white blood count, age, and cell morphology. Remission is induced with prednisone, vincristine and L-asparaginase in all children and similar CNS prophylaxis is given to all except the good-risk group which is randomized to either intrathecal methotrexate or cranial irradiation and intrathecal methotrexate. All patients are then randomized for various maintenance programs to answer the question of whether it is advantageous to 1) give further intermittent intrathecal methotrexate and 2) various intermittent additive drugs to systemic chemotherapy with daily 6-mercaptopurine and weekly methotrexate orally.

Children with acute non-lymphocytic leukemia are induced with continuous infusion cytosine arabinoside for 7 days plus 3 daily doses of adriamycin, given at 2 week intervals. If remission is obtained, children with HLA sibling matches will receive bone marrow transplant. Those without such matches will enter a chemotherapy maintenance program involving cyclic versus continuous use of multiple agents.

Solid tumor studies include the intergroup studies for Wilms' tumor, Ewing's sarcoma and rhabdomyosarcoma. Studies for Stage I and II Hodgkin's disease and non-Hodgkin's lymphoma are being done in conjunction with other cooperative groups. Other Children's Cancer Study Group studies are current for brain tumors, osteogenic sarcoma, histiocytosis X, retinoblastoma, liver tumors and ovarian tumors.

BIBLIOGRAPHIC REFERENCES: Heidelberger, K.P., Schnitzer, B., Tilford, D., Poznanski, A.K., and Heyn, R. Marked skeletal involvement in sinus histiocytosis with massive lymphadenopathy. Accepted for publication in Skeletal Radiology, May, 1979. Lahey, M.E., Heyn, R.M., Newton, W.A. Jr., Shore, N., Smith, W.B., Leikin, S., and Hammond, D. Histiocytosis X: Clinical trial of Chlorambucil. A report from Children's Cancer Study Group. Accepted for publication in Medical and Pediatric Oncology, 1979.

325. UNIVERSITY ONCOLOGY PROGRAM

Bagshaw, M. A., Rosenberg, S. A., Martinez, A., Coleman, C. N., Jacobs, C., Kempson, R., Fee, W., Stockdale, F., Sikic, B., Stanford University, School of Medicine, Dept. of Radiology, *300 Pasteur Dr., Stanford, California*, 94305, United States of America

This proposal is for the continuation of Stanford participation in the Northern California Oncology Group (NCOG) for a multi-institutional cooperative study of the multi-modality treatment of a variety of neoplasms. The multi-modality studies will include various combinations of surgery, radiation therapy, and chemotherapy, used either as adjuvants or as primary treatment in carcinoma of the breast, bronchus, gastrointestinal tract, urinary bladder, prostate, non-seminoma-testicular neoplasms, ovarian carcinoma, cervical carcinoma, endometrial carcinoma, epidermoid carcinoma of the head and neck and melanoma. Stanford intends to participate in almost all of the active programs which, it is estimated, will number about 30 at any given time. Special features of the Stanford participation will include an extramural network of participating medical oncologists, the use of our oncology day care center for the administration of chemotherapeutic agents on an out-patient basis and the use of our clinical research center (CRC) for in-patient hospitalization in support of protocols approved by the CRC advisory board. In addition to clinical participation Stanford intends to use its radiobiology facilities for further studying radiotherapeutic and chemotherapeutic interactions, hyperthermia, and radiation sensitizers.

326. VETERANS ADMINISTRATION SURGICAL ONCOLOGY GROUP

Higgins, G. A., White, G. E., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Surgical Service, *50 Irving St. N.W., Washington, District of Columbia*, 20422, United States of America

In 1978 the group changed its name to the Veterans Administration Surgical Oncology Group and is now in its 22nd year, during which time over ten thousand patients, mostly with carcinoma of the lung, stomach and large bowel have been entered into a large variety of protocols for the studies of the possible effects of adjuvant chemotherapy, radiotherapy and immunotherapy in patients having surgical resection. During calandar year 1978 a total of 575 patients were entered into the current protocols. Of these 199 were entered into the three protocols studying large bowel cancer, 145 into the lung cancer protocol and 64 in the gastric cancer protocol. The remaining patients were entered into studies on carcinoma of the pancreas, esophagus and head and neck. These latter protocols were discontinued during the year except for recording of patients with carcinoma of the pancreas and a pilot study in head and neck cancer conducted by two of the hospitals in the study group.

Currently three new protocols are being developed, two for patients with lung cancer, one of which used nonspecific BCG immunotherapy in patients with negative nodes and the other utilizing postoperative radiotherapy in patients having resection but with positive lymph nodes in the specimen; the third protocol is a continuation of the trial on patients with carcinoma of the colon. All patients will receive two courses of 5-FU following operation and will then be randomized into one of three arms: no further medication; intermittent courses of 5-FU for eighteen months; a combination of 5-FU and hydroxyurea for an eighteen month period. These three protocols should be activated within three weeks.

327. SUPPORT OF CANCER AND LEUKEMIA GROUP B STUDIES

Berenberg, J. L., Taylor, G., Weltz, M., Holloway, H., D'Avis, J., Karcher, D., Neglia, W., Detrick Hooks, B., U.S. Dept. of Defense, Army, Medical Research & Development Command, *c/o Walter Reed Army Med. Ctr., Washington, District of Columbia*, 20310, United States of America

OBJECTIVE: To investigate the treatment of adult patients with neoplastic diseases. This study involves consideration of investigational and standard drugs, radiotherapy, psychiatric evaluation, and design of surgery. Furthermore, it strives to analyze the contribution of pathology and immunology to the clinical treatment of cancer patients. Patients at Walter Reed Army Medical Center (WRAMC) are entered on Cancer and Leukemia Group B (CALGB) protocols. Goals for the coming year include: formulating phase II and phase III protocols for head and neck cancer and testicular carcinoma studies; initiating a controlled study in the use of intravenous immunoglobulins in patients at high risk for infection; and completing an adriamycin pharmacokinetic study to determine whether indocyanine green clearance will predict the ability of the liver to clear this chemotherapeutic agent.

328. SOUTHWEST ONCOLOGY GROUP

Coltman, C. A., Cruz, A. B., Mira, J., Rappaport, E. S., University of Texas, Health Science Center at San Antonio, Medical School, Dept. of Medicine, *7703 Floyd Curl Dr., San Antonio, Texas*, 78284, United States of America

This cancer research program will be carried out in cooperation with the other members of the Southwest Oncology Group. It involves the combined modality (medical oncology, surgical oncology, radiation oncology, and pathology) approach to the management of adults with malignant disease. The principal investigator and other participants have broad experience in cooperative therapeutic research. The project is conducted at the University of Texas Health Science Center and, by subgrant, the Cancer Therapy and Research Center. The participants are involved in protocol design of Phase I, II, and III studies in chemotherapy research as well as in combined modality research. The principal investigator (Charles A. Coltman, Jr.) is chairman of the Leukemia Committee, and Chairman of the Disease and Discipline Committee of the Group. One co-principal investigator (Anatolio B. Cruz, Jr.) is co-chairman of the Head and Neck Cancer Committee and active in the reorganization of the Surgical Oncology Committee. Our radiation oncology members have contributed over 60 combined modality patients to group studies.

BIBLIOGRAPHIC REFERENCES: Coltman, C.A., Jr.: Hodgkin's disease: Chemotherapy. In Current Therapy, H.F. Conn, Ed. W.B. Saunders, Co., Philadelphia, pp. 281-286, 1979. Mullins, J.D., Newman, R.K., and Coltman, C.A., Jr.: Primary oat cell carcinoma of the larynx: A case report and review of the literature. Cancer 43:711-717, 1979.

329. INTERGROUP RHABDOMYOSARCOMA STUDY

Maurer, H. M., Ruymann, F., Sutow, W. W., Raney, R. B., Lawrence, W., Ragab, A. H., Virginia Commonwealth University, Medical College of Virginia, Dept. of Pediatrics, *1200 E. Broad St., Richmond, Virginia,* 23298, United States of America

The Intergroup Rhabdomyosarcoma Study (IRS), a collaborative effort of Children's Cancer Study Group, and Southwest Oncology Group, is a multi-disciplinary study designed to answer important questions about the treatment and biological characteristics of rhabdomyosarcoma in childhood and adolescence. Initiated in November, 1972, IRS-I closed to patient entry in November, 1978, and IRS-II began. Data obtained in IRS-I bear on the surgical, radiotherapeutic, and chemotherapeutic aspects of treatment in relation to disease stage and primary site of tumor origin. Information of prognostic value relative to histology, primary site and sex emerged. Two new histologic subtypes plus patterns of disease spread in relation to primary site, of importance in design of new treatment regimens, have been identified. Two-year disease-free survival rates in IRS-I are 89-90 percent in Group I, 70-75 percent in Group II, 60-65 percent in Group III, and 30 percent in Group IV.

Developed as an outgrowth of IRS-I, IRS-II has as its major goals to further refine treatment in Group I; increase disease-free survival rates in Groups II-IV with prolonged intensive chemotherapy, and more aggressive radiation in Group IV: prevent CNS extension from head and neck sites with radiation and chemotherapy; assess primary chemotherapy vs. primary surgery for GU tumors; develop a pathologic staging classification.

As in IRS-I, IRS-II will be monitored by a multi-disciplinary steering committee composed of surgeons, radiotherapists, chemotherapists, pathologists and biometricians representing the two participating cooperative cancer treatment groups.

BIBLIOGRAPHIC REFERENCES: Raney, R.B., Jr., Gehan, E.A., Maurer, H.M., Newton, W.A., Jr., Ragab, A.H., Ruymann, F.B., Sutow, W.W., and Tefft, M. (For the Intergroup Rhabdomyosarcoma Study Committee). Evaluation of Intensified Chemotherapy in Children with Advanced Rhabdomyosarcoma (Clinical Groups III and IV). Clinical Ca. Trials Spring 1979, p. 19-28.

330. SOUTHWEST ONCOLOGY GROUP

Rivkin, S. E., Tesh, D. W., Wasserman, P., Hibbs, G., Roth, G., Stutz, F. H., Johnson, L., Witherspoon, R., Milder, M., Gottesman, J., Novack, A., Hoffman, H. C., Swedish Hospital Medical Center, Dept. of Epidemiology & Public Health, *747 Summit Ave., Seattle, Washington,* 98104, United States of America

The objective of these studies is to refine and improve cancer therapy. Improvement can be obtained by reducing treatment toxicity and improving both host resistance to neoplasm and the responsiveness of a disease to treatment. To this end multiple modalities including surgery, chemotherapy, radiation therapy and immunodiagnosis are used in the common protocols of the Southwest Oncology Group.

The goals of the coming year include active participation in all Southwest Oncology Group activities. The Pacific Northwest investigators have shown particular interest in protocols on breast cancer, lung cancer, sarcoma, head and neck cancer, and mycosis fungoides.

BIBLIOGRAPHIC REFERENCES: Rivkin, S.E., Gottlieb, J.E., Thigpen, T., Elsebai, I: Methyl CCNU-adriamycin in metastatic sarcomas. Proc. Am. Soc. Clin. Onc., 20:331, 1979 (Abstr. C-97). Alberts, D.S., Hilgers, R.D., Moon, T.E., Martimbeau, P.W., Rivkin, S.E.: Combination chemotherapy for alkylator-resistant ovarian carcinoma: a preliminary report of a Southwest Oncology Group trial. Cancer Treat. Rep. 63:301-305, February 1979.

331. CLINICAL TRIALS - EASTERN COOPERATIVE ONCOLOGY GROUP

Merrill, J. M., Williams, R. M., Gordon, L., Ozer, H., Kies, M., Vriesendorp, H., Grumet, G., Oviedo, M., Northwestern University, Chicago Campus, School of Medicine, Dept. of Medicine, *303 E. Chicago Ave., Chicago, Illinois,* 60611, United States of America

Members of Northwestern University Medical School, within the Northwestern University Cancer Center, will continue to participate in the activities of the Eastern Cooperative Oncology Group (ECOG). Project participants have identified areas for local pilot study development projects, including genitourinary cancer and malignant lymphomas.

BIBLIOGRAPHIC REFERENCES: Bianco, A., Merril, J., et al. Combination chemotherapy in head and neck squamous cancer, Cancer Treatment Reports, 63, 158-159, 1/79. Kisielius, T., Bianco, A., Merrill, J., et al. Bleomycin in combination chemotherapy of metastatic Wilms' Tumor, Medical and Pediatric Oncology, 6, 11-14, 1979.

332. EASTERN COOPERATIVE ONCOLOGY GROUP

Kaplan, B. H., Vogl, S. E., Escher, G., Volk, H., Ghossein, N., Janis, M., Axelrod, M., Campbell, P., Greenwald, E., DiPillo, F., Geraty, M., Camacho, F., Yeshiva University, Bronx Campus, Albert Einstein School of Medicine, Dept. of Medicine, *1300 Morris Park Ave., Bronx, New York,* 10461, United States of America

The Albert Einstein College of Medicine will continue to participate in the activities of the Eastern Cooperative Oncology Group, in all phases. AECOM will put substantial numbers of patients into groupwide cooperative trials; it will design and carry out pilot studies to test new regimens for possible groupwide application, and members of its faculty will assist in committee activities for the ECOG.

Investigators from AECOM are directing groupwide trials in head and neck carcinoma, ovarian cancer, and small cell cancer of the lung. AECOM remains the largest contributor of patients to approved ECOG-pilot studies. Currently pilot studies are underway in esophageal, cervical, head and neck, and ovarian cancer, and proposals for new pilot studies in breast, gastric and colorectal cancer are under consideration.

BIBLIOGRAPHIC REFERENCES: Vogl, S., Kaplan, B. Chemotherapy of Advanced Head and Neck Cancer with Methotrexate, Bleomycin, and Cis-diamminedichloroplatinum II in An Effective Outpatient Schedule, Cancer, 44:26-31,1979. Vogl, S., Zaravinos, T., Kaplan, B. Toxicity of Cis-diamminedichloroplatinum II Given in a Two-Hour Outpatient Regimen of Diuresis and Hydration, Cancer, 45: 11-15, 1980.

333. EASTERN COOPERATIVE ONCOLOGY GROUP

Creech, R. H., Engstrom, P. F., Strawitz, J., Richter, M., Fox Chase Cancer Center, *7701 Burholme Ave., Philadelphia, Pennsylvania,* 19111, United States of America

Through the Eastern Cooperative Oncology Group (E.C.O.G.), The American Oncologic Hospital (A.O.H.) of the Fox Chase Cancer Center is attempting to improve the quality and duration of cancer patients' lives by developing and scientifically evaluating the most effective treatment regimens for all types of cancer. The A.O.H. has four principal objectives as related to the E.C.O.G.: 1. To maintain high patient accrual on E.C.O.G. protocols by organizing disease-oriented multidisciplinary committees which will be responsible for developing protocol priorities and treating patients with malignancies being studied by the E.C.O.G. and by the A.O.H. 2. To maintain the high quality of protocol patient evaluation by delegating responsibility for data management to one surgical, one radiation therapy, and two medical protocol coordinators. 3. To pilot multimodal surgical, radiation therapy, and chemotherapy trials, particularly in lung, gastrointestinal, and head and neck cancer. 4. To participate in protocol development through E.C.O.G. committee membership.

334. EASTERN COOPERATIVE ONCOLOGY GROUP

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The major objectives are the overall objectives of the ECOG. These include: 1) The early evaluation of anti-cancer compounds. 2) The pharmacology, toxicology and efficacy of such compounds. 3) The acquisition of knowledge concerning the biology and patterns of expression of malignant disease.

Of additional particular interest to the principal investigator is: 1) Combination therapy (chemotherapy plus concomitant radiotherapy) in the management of locally advanced cancer. 2) The early chemotherapy of cancer when present but not yet measurable. 3) Large dose multi-drug chemotherapy of advanced cancers. 4) Interdisciplinary approach to care of the cancer patient. 5) Treatment of metastatic breast cancer with anti-estrogens (Tamoxifen) and its correlation to estrogen receptor proteins. 6) The use of WBC transfusions in septic, neutropenic patients. 7) The use of central and peripheral hyperalimentation in patients receiving multi-modal therapy, especially advanced head and neck cancers.

BIBLIOGRAPHIC REFERENCES: Vogl, S., McCormick, B., Coughlin, C., Lerner, H., and Kaplan, B. Chemotherapy with Cis-Platinum, Methotrexate and Bleomycin As Initial Treatment for Regionally Advanced Head and Neck Cancers. Submitted for presentation at the 62nd Annual Meeting of the American Radium Society, Philadelphia, PA, April 1980. Lerner, H., Carbone, P., and Kalbfleisch, J. Intermittent Parenteral Methotrexate (EST 2365). Submitted for presentation at the 16th Annual Meeting of the American Society of Clinical Oncology, San Diego, CA. May, 1980.

335. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) AND WISCONSIN CLINICAL CANCER CENTER (WCCC) RESEARCH PROTOCOLS

Borden, E. C., Walker, K. L., Freeberg, B. L., Shoaf O'Kula, H. K., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *2500 Overlook Ter., Madison, Wisconsin*, 53705, United States of America

Currently, 23 ECOG and 12 WCCC protocols are active through the Division of Clinical Oncology. Since the initial report was filed, the VA has begun participating in Phase I trials. A phase I-II protocol for the evaluation of interferon given intra-muscularly and intra-arterially has recently been approved by the Subcommittee for Human Subjects and accrual will begin as soon as eligible patients are identified.

336. RADIATION THERAPY ONCOLOGY GROUP

Fu, K. K., Phillips, T. L., Luk, K., Hill, D., University of California, San Francisco Campus, School of Medicine, Dept. of Radiation Oncology, *551 Parnassus Ave., San Francisco, California*, 94122, United States of America

Support requested in this application is for the ongoing and expanding participation of the Department of Radiation Oncology of the University of California in San Francisco in the activities of the Radiation Therapy Oncology Group. Comprised of three hospitals, Moffitt, Mt. Zion and Franklin, the Department is staffed by eleven full-time faculty members, treating 2000 new patients per year. The Department has participated in the Group since 1972, entering approximately 150 patients into the various Group protocols, pilot studies and registry protocols during the last year. The Principal Investigator is a member of the Head and Neck Committee, Combination Radiotherapy and Chemotherapy Sub-Committee and Hematopoietic Sub-Committee of the Radiation Therapy Oncology Group. The Associate Principal Investigator is Chairman or the Radiobiology Committee and a member of the Publication Committee, Experimental Design Committee, Lung Sub-Committee, Metastases Sub-Committee, Radiation Injury Sub-Committee, Hyperthermia Sub-Committee and Chairman of the Radiosensitizer/Protector Committee and all staff members serve on the working parties. The group has produced protocols for head and neck cancer, non-Hodgkin's lymphoma, brain metastasis, and hypoxic cell sensitizers, as well as providing input into other protocols. Support through this application will allow RTOG participation by the entire Department and its affiliated institution, the University of California, San Diego, Division of Radiation Oncology and increase the case accession rate to 175-200 new patients per year into the various RTOG protocols. Extensive continuing research into chemical and thermic modification of radiation effects and high LET radiotherapy is expected to lead to innovative protocols and correspondingly to increased accession of patients into studies sponsored by the RTOG.

337. FERMILAB CANCER THERAPY FACILITY

Cohen, L., Awschalom, M., Hendrickson, F., Rosenberg, I., Hrejsa, A., Kaul, R., Mansell, J., Zimmer, D., Bennett, B., Pientak, B., Universities Research Assn. Inc., *2100 Pennsylvania Ave. N.W., Washington, District of Columbia*, 20037, United States of America

The overall objective of the study is to continue a major research program for clinical trials in fast neutron therapy in order to evaluate the effectiveness of neutron therapy relative to other forms of conventional radiation therapy. Since all essential preclinical physical measurements and calibration, radiobiological studies, and pilot studies on patients referred with locally advanced disease have been completed satisfactorily, our objective at this stage is a strictly controlled experiment within a cooperative national protocol to evaluate one modality against another in randomly selected groups of patients. This work will concentrate mainly on subjects eligible for entry into the RTOG protocols: Resectable and Nonresectable Late Stage Cancer of the Head and Neck, Malignant Brain Tumors, Cancer of the Prostate and Bladder, Late Stage Carcinoma of the Cervix, Carcinoma of the Esophagus, Small Cell Carcinoma of the Lung, Carcinoma of the Pancreas, Tumors of Salivary Glands, Radioresistant Adenocarcinomas, Bone and Soft Tissue Sarcomas.

338. RADIATION THERAPY ONCOLOGY GROUP

Perez, C. A., Washington University, School of Medicine, Dept. of Radiology, *660 S. Euclid Ave., St. Louis, Missouri*, 63110, United States of America

The Division of Radiation Oncology at Washington University proposes to: 1) Continue participation in clinical trials of the Radiation Therapy Oncology Group; 2) contribute to the scientific contents of group studies and to actively engage in protocol design and coordination; 3) assist in administrative and organizational matters of the group outlined by the Chairman of the Group and Committee Chairmen; 4) participate in the analysis of scientific data generated by the Radiation Therapy Oncology Group and to prepare manuscripts to be submitted for publication to reputable scientific journals; 5) promote clinical trials within the framework of cooperative groups at Washington University School of Medicine. The Division has consistently been one of the major contributors of patients to RTOG protocol studies. Approximately 50% of the patients accessioned to the studies have been in non-metastatic protocols. The projected number of patients to be entered in protocol studies during the year 1979 will be in the range of 90 to 100. The Division participates in the avant-garde protocols in radiation oncology that require specialized facilities and equipment such as the hyperthermia and hypoxic sensitizers.

339. RADIATION THERAPY ONCOLOGY GROUP

Rubin, P., University of Rochester, School of Medicine & Dentistry, Dept. of Radiation Oncology, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

The RTOG is a cooperative group of radiation therapy research and clinical centers organized for the purpose of conducting joint clinical investigations. The Division of Radiation Oncology of the University of Rochester Cancer Center is one of the member institutions of the RTOG, and the Offices of Protocol Design and of the Vice-Chairman are located within it. A listing of the major RTOG objectives and progress that has been made by the group, both nationally and at this institution, is described and includes: case accession, new research areas, standardized treatment planning, quality control, neutron clinical investigation, study registries and forms, and the interaction of the RTOG with other cooperative groups. The protocol design activities of the RTOG are reviewed through two schemes: First, major radiation themes which can apply to many disease sites: time dose factors, radiosensitizers, systemic irradiation, high LET irradiation, optimal time of radiation therapy and chemotherapy, hyperthermia, combining innovations in radiation therapy and mathemtical modeling; second, disease sites in terms of unique specific studies, especially studies of brain, lung, head and neck, genitourinary and metastatic disease. The activities of the Division of Radiation Oncology in protocol accession and the studies which are chaired by members of this institution are reviewed.

340. RADIATION THERAPY ONCOLOGY GROUP

Goodman, R. L., Bloch, P. H., Carabell, S. C., Richter, M. P., Alavi, J., University of Pennsylvania, School of Medicine, Dept of Radiation Therapy, *36th & Hamilton Walk, Philadelphia, Pennsylvania*, 19174, United States of America

The University of Pennsylvania (UP) is a member of the Radiation Therapy Oncology Group (RTOG). It not only contributes large numbers of patients, especially those with head and neck tumors, but both radiation therapy and non-radiation therapy specialists contribute time and effort in committee work and in providing consultative services. UP soon will also initiate clinical and radiobiology neutron beam research under RTOG guidelines. Thus, the UP exemplifies in its activities a commitment to interdisciplinary approach to patients with oncological disease and assists RTOG, a cooperative group of radiation therapy research and clinical centers, in the conduct of joint clinical investigation. The group conducts randomized clinical trials and other cooperative clinical studies to advance knowledge in the cure and control of cancer by gathering adequate numbers of patients necessary for the answer to important clinical questions. It also makes possible the collection of long-term data with regard to radiation complications and patient survival, and promotes multi-disciplinary care by integrating its study programs with those of other disciplines. In that way, it also enriches training programs in oncology as well as radiation therapy.

341. RADIATION THERAPY ONCOLOGY GROUP

Marks, R. D., Fitzgerald, R. H., Moore, T. N., Wallace, K. M., Adkins, W. Y., Medical University of South Carolina, School of Medicine, Dept. of Radiation Therapy, *80 Barre St., Charleston, South Carolina*, 29401, United States of America

Support is requested in this application for expanding the participation of the Division of Radiation Oncology of the Medical University of South Carolina in the activities of the Radiation Therapy Oncology Group. This department participates in radiation oncology programs at the Medical University of South Carolina and affiliated Roper Hospital in Charleston. The Division treats approximately 1200 patients a year, 1000 of these being new cancer patients. The Radiation Oncology Division has participated in the Radiation Therapy Oncology Group since 1973 and has been an active member since January 1974. Subsequent to the data above, approximately 200 cases have been accessioned into the various protocols of the Radiation Therapy Oncology Group. The Principal Investigator has been active in attending all meetings since 1974 and recently was appointed a member of the Site Visit Committee and a member of the Nominating Committee for the Group. The Principal Investigator has been an active participant in all working parties and has recently authored a Pilot Study involving hyperfractionation. To date the Division has entered a number of patients in the Lung Protocol, a split course protocol, mainly involving patients with carcinoma of the cervix, and the Head and Neck Protocol. At the present time we have submitted a contract proposal for the proposed study involving chemotherapy, radiotherapy, and surgery in treatment of advanced carcinoma of the head and neck.

342. SAFER CANCER CHEMOTHERAPY - THE DESIGN OF MULTIPLE DRUG PROTOCOLS (ABBREV)

Hill, B. T., Price, L. A., Imperial Cancer Research Fund, Cellular Chemotherapy Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

The use of antitumor drugs has traditionally been reserved for patients who fail to respond or whose tumors have recurred after standard treatment with radiotherapy and surgery. This understandable reluctance to use chemotherapy, except as a last resort, derives from the mistaken belief that drug therapy is automatically associated with severe toxicity. We have shown that, provided certain precautions are observed, it is possible to administer intensive combination chemotherapy protocols, designed according to certain kinetic principles (see ICRF Scientific Report 1976 - report 59), with safety and without loss of therapeutic benefit. This approach, involving treatment over 24-36 hours rather than several days, has been used effectively against certain advanced malignancies. For example, head and neck cancers (ICRF Scientific Report 1978 - report 18), breast carcinomas (Goldie and Price, British Medical Journal, 1977, 2, 1064) and non-squamous cell lung cancers (Anderson et al. British Journal of Diseases of the Chest, 1977, 71, 179). Ongoing studies include the treatment of advanced endometrial carcinomas (ICRF Scientific Report 1978 - report 20) where 2/6 responses have been noted and pancreatic tumors (in collaboration with Dr. J. Angers, New York, USA) involving treatment with vincristine, mitomycin C, procarbazine, chlorambucil, 5-fluorouracil and pyrimethamine.

Recently we have designed trials based on these principles, for cervical cancer in collaboration with Johannesburg, and for prostatic cancer for the Multicentre U.K. trial. These protocols are all well tolerated by the patients and allow a good quality of life. This safe and effective method of administering combination chemotherapy can now be used to complement local therapy.

343. A PROGRAM IN MEDICAL ONCOLOGY

Cline, M. J., University of California, Los Angeles Campus, School of Medicine, Dept. of Medicine, *2025 Zonal Ave., Los Angeles, California*, 90024, United States of America

The research programs in the Division of Hematology-Oncology will continue to encompass four program areas: 1) chemotherapy-immunotherapy of selected malignant diseases (acute leukemia, lymphoma, lung, breast, and head and neck cancer); 2) allogeneic and autologous bone marrow transplantation in combination with intensive chemoradiotherapy; 3) studies of normal and malignant hematopoiesis; 4) studies of host defense mechanisms against microorganisms and neoplastic cells.

344. COORDINATED REGIONAL CANCER CONTROL PROGRAM

Steiner, J. W., Hendrickson, F., Berlin, N., Brewer, J., Illinois Cancer Council, Division of Cancer Control, *36 S. Wabash Ave., Suite 700, Chicago, Illinois*, 60603, United States of America

The Illinois Cancer Council was designated as a comprehensive Center in 1974 and awarded a Center planning grant and a control Program support grant. Exploratory studies of feasibility were not completed until late 1977 and the Center received NCI Core funding in December 1978. A full-time Director was appointed, effective January 1979. The Center is a consortium of 12 medical schools and other Illinois institutions bound by agreement to implement a regional cancer program. The executive Committee acts as the Advisory Committee on Cancer Control to the Governor of Illinois and it liaises with the Health Systems Agencies and the Statewide Health Coordinating Council on strategic issues of cancer programs and resources in the region. Control and education projects initiated during the planning phase include regional cooperative clinical trials in gynecology (GOG), radiation therapy (RTOG), and neutron therapy at the Fermilab, a Pediatric Outreach Project, a Study of Utilization of Rehabilitation Services, a Demonstration Communications Network (CIS), a Network Demonstration Project for Head and Neck Cancer and the development of a consortial database and related biostatistical and epidemiological support services and studies. Planning will aim at systematizing Control and Education programs. They will include outreach initiatives through extended regional cooperative clinical trials, activities to a broad spectrum of community hospitals, evaluative studies of Control programs and an analysis of network systems, rehabilitation programs particularly relating to the Head and Neck Network Study and initial approaches to epidemiologic and detection studies. Underlying these thrusts will be emphasis on bridging cancer programs among the affiliated cancer centers and major research centers and with community hospitals through model Networks planned, coordinated and evaluated by the Center. This application is for support of Headquarters to carry out coordinated planning and implementation of outreach, education, rehabilitation, detection and related activities and for seed funding to implement pilot developmental projects in Cancer Control.

345. HEAD AND NECK CANCER PATIENT MANAGEMENT

Warnecke, R. B., Illinois Cancer Council, *36 S. Wabash Ave., Suite 700, Chicago, Illinois*, 60603, United States of America

OBJECTIVE: Synthesize the information and experiences of the six network demonstration projects in head and neck cancer to facilitate the transfer of the current knowledge, skills, and technology gained from the projects in a meaningful, concise, operational form to the health professional community.

346. TREATMENT OF DIFFERENTIATED AND ANAPLASTIC THYROID CANCERS

DeGroot, L. J., University of Chicago, Pritzker School of Medicine, Dept. of Medicine, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

This is part of a broader project. A summary of this subproject is not available.

347. CANCER CENTER SUPPORT (CORE) GRANT

Holland, J. F., Bekesi, J. G., Ohnuma, T., Suzuki, Y., Hirschhorn, K., Desnick, R. J., Roboz, J., Glidewell, O., Goldberg, J., Norton, L., Gerber, I., City University of New York, Mount Sinai School of Medicine, School of Medicine, Dept. of Neoplastic Diseases, *1 Gustave L. Levy Pl., New York, New York*, 10029, United States of America

Administration of the activities of the Mount Sinai Cancer Center is developed around coordination of the major programs in the Center of clinical and fundamental nature to achieve maximum productivity among the many departments participating in the undertaking.

Patient availability continues to be satisfactory through private referral, from the Departments of Surgery and Gynecology, Radiotherapy, Head and Neck Surgery, chest medicine and many of the private oncologists. Consultation is broad-scoped and many of the private medical oncologists interact with the Department in patient consultation and referral as well as in monthly meetings of medical oncology to implement protocols of the Center in circumstances of patients with metastatic disease and in those with surgical adjuvant treatments of cancer in which surgeons and medical oncologists consent.

Planning activities have also been undertaken intramurally within the Center in periodic conferences, involving relevant surgical, radiologic and medical oncologic specialties for protocol development. Examples of this include studies in ovarian cancer, cervical cancer, head and neck cancer, acute leukemia and breast cancer. In all these diseases new multi-disciplinary programs have been inaugurated.

Biostatistical participation has advanced substantially in its interrelationship with the programs of the Center. Design of protocols, the randomization of patients, the analysis of all data and the preparation of materials for presentation is uniformly a concern of clinical biostatistics studies. Many select laboratory investigations are also subject to this level of biostatistical input, and there has been a steady and palpable improvement in quality and surety of results. This application is submitted for continued support for the administration of the Cancer Center.

348. HEAD AND NECK CANCER

Wittes, R., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

349. CLINICAL CANCER RESEARCH PROGRAM

Drezner, M., Seigler, H. F., Huang, A. T., Paulson, D., Metzgar, R., Lyles, K., Laszlo, J., Duke University, School of Medicine, Dept. of Medicine, *Box 3711, Durham, North Carolina*, 27710, United States of America

This program project renewal application seeks support for multidisciplinary clinical research projects dealing with proposals for new methods of diagnosis and treatment of cancer. The leukemia-lymphoma program has projects in autologous bone marrow transplantation, childhood ALL, studies of newly described morphologic particles, research on lymphoproliferative and myeloproliferative disorders, leukemia immunology, platelet antigens, and biochemical pharmacologic studies of new lipid soluble folate antagonists. Additional programs are described in urologic oncology, which include a range of projects from ultrastructure, culture of human cells and clinical chemotherapy through to metabolic studies of new findings of tumor induced osteomalacia, and prognostic factors in prostatic cancer. Interdisciplinary programs in lung cancer, head and neck cancer, breast cancer, malignant melanoma, and brain tumors are also presented in this application.

The central feature of this request is that we have a newly constructed facility in which multidisciplinary research can be conducted and which provides the optimal conditions for education and patient care and enables the collection of research materials for laboratory investigations. The clinical faculty has been greatly expanded and the scope of research increased accordingly.

350. UNIVERSITY OF PENNSYLVANIA CANCER CENTER PROTOCOLS

Negendank, W., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *38th & Woodland Aves., Philadelphia, Pennsylvania*, 19104, United States of America

Ongoing studies at this time include adjuvant chemotherapy trials for carcinoma of the head and neck, use of a radioprotector drug to allow higher doses of radiation and chemotherapy to be delivered to the tumor, and studies of patient and family participation in the treatment-decision process.

351. CANCER CENTER SUPPORT GRANT

Cooper, R. A., University of Pennsylvania, School of Medicine, Dept. of Medicine, *36th & Hamilton Walk, Philadelphia, Pennsylvania*, 19174, United States of America

The University of Pennsylvania Cancer Center (UPCC) study is a multidisciplinary program in cancer research, education and clinical care. Based in the School of Medicine, it involves faculty from many schools of the University. The UPCC is one component of the Fox Chase-U. of P. Comprehensive Cancer Center. Interdisciplinary clinical research programs of the UPCC exist in hematology-oncology, radiation therapy, surgical oncology and gynecologic oncology. A multidisciplinary program has been established in head and neck tumors, and similar programs are developing in neuro-oncology and urologic cancer. Clinical research programs utilize the shared resources of the Center's inpatient Oncology Study Unit, Clinical Trials Data Center, Pharmacology Core and Nutrition Support Service. Interdisciplinary fundamental research programs exist in immunobiology, cell biology, virology, genetics, and radiobiology. Program development involving tumor immunology and bone marrow culture is planned. Fundamental research programs utilize the shared resources of an animal breeding colony and tissue culture core, and they are strengthened by a Visiting Scientist Program. Acquisition of a fluorescence activated cell sorter is also planned. The Center's Epidemiology and Statistics Unit includes epidemiologic studies of occupational carcinogenesis and biostatistical research. The Unit established a biostatistics shared resource for the UPCC and a patient data system compatible with the CCPDS. A multidisciplinary Psychosocial Program, recently established, addresses needs in areas of research, service and education. Other Educational Programs have been established as well, and the UPCC provides a range of opportunities for medical and nursing students, fellows, practicing physicians and other health professionals. The UPCC Cancer Control Program extends to community hospitals in Pennsylvania and New Jersey. An information letter, Cancer Update, provides UPCC news and cancer education for Center members and other professionals who relate to the UPCC.

352. HEAD AND NECK CANCER

Lindberg, R. D., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Radiotherapy, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

This is part of a broader project. A summary of this subproject is not available.

353. CANCER CENTER SUPPORT - COMPREHENSIVE

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The Wisconsin Clinical Cancer Center is a University-based comprehensive cancer center dedicated to patient oriented laboratory and clinical cancer research, multidisciplinary care, and professional and public education. The WCC has an academic home in the Medical School and Center for Health Sciences with 45 professional members in the Department of Human Oncology. The Center also serves as a focal point for cancer research and patient care for other departments in the Medical School, providing financial, intellectual, and physical facilities for a large number of associate members. A close relationship exists with these other departments in regard to cancer activities.

The WCCC is responsible for major clinical research programs with multidisciplinary trials for breast, pancreas, lung, melanoma, and genitourinary cancers. Laboratory research programs include etiology, pharmacology, radiobiology, endocrinology, immunology and genetics. Outreach programs include many professional and non-professional educational activities, as well as diagnostic and management networks for colposcopy and head and neck cancer. Future ares of emphasis will include strengthening of current programs, as well as development of new effforts in somatic cell genetics, nutrition and preventive oncology.

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CURRENT CANCER RESEARCH PROJECT REGISTRATION FORM

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National Cancer Institute
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